(See Soper letter to Soper, Februar[illegible]

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FACTORS WHICH SHOULD DETERMINE THE SELECTION OF AN ANTHELMINTIC IN A GEOGRAPHICAL AREA.*

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The most important factors which influence the choice of an anthelmintic † for field work are: efficiency, toxicity, ease of administration, and cost of the standardized drug. Special local conditions which may affect one or more of these factors are: the degree and character of the local hookworm infestation; the degree of infestation with other parasites, especially *Ascaris;* the alcoholic habits of the people; the distribution of population; the presence of malaria; and the character and aim of the local campaign. *Ancylostoma* is notoriously more resistant to chenopodium and thymol than is *Necator* (Darling, et al., 1). The same has been reported for carbon tetrachloride (Smillie and Pessoa, 17) (Sawyer and Sweet, 15). Fatal cases of intoxication have been reported in children harboring *Ascaris* and treated with carbon tetrachloride (Lambert, 7). Carbon tetrachloride has been found to be toxic for alcoholics. Where the population is widely scattered the necessity of dividing the dose and administering a delayed purge may easily double or treble the cost of administration. A local campaign based on the dispensary plan may be able to use a method of treatment which would not be suitable for house to house campaigns. If the end sought is a rapid reduction of soil pollution, an anthelmintic with selective action against females might be chosen in preference to one with selective action against males. The presence of malaria is probably of importance only, if beta-naphthol is the anthelmintic under consideration, when the toxicity may be enhanced (Smillie, 16).

Work in recent years has practically reduced the choice of an anthelmintic for field work to oil of chenopodium, carbon tetrachloride, or some combination of these two.

The writer in January, 1924, faced the problem of selection of an

* This report is based on experimental and field work carried out as part of the campaign against hookworm disease in Paraguay, conducted with the financial cooperation of the International Health Board and the Republic of Paraguay.

† The word 'anthelmintic,' when used in the present report, will refer to drugs employed for their action on hookworms, unless otherwise stated.

anthelmintic for field work in an area where, with a high known rate of infestation, the degree and character of hookworm infestation was unknown; where the *Ascaris* rate (percentage of population infested) was calculated at five per cent.; where alcohol is widely and freely used; where the population is largely rural, and where the program of the local campaign called for the treatment of all families in their homes. After reviewing the then available published reports of the use of carbon tetrachloride and oil of chenopodium, a three to one mixture of these drugs in adult dosage of 2.4 c.c., with delayed purge of magnesium sulphate after two hours, was adopted as the standard treatment for hookworm disease in the Campaña Sanitaria of the Republic of Paraguay. This standard treatment has since been altered to a two to one mixture of carbon tetrachloride and oil of chenopodium in adult dose of 2.4 c.c., with simultaneous purge of magnesium sulphate in concentrated solution. This report is based on the carefully controlled experiments which led to this change of treatment for Paraguayan conditions.

Several tests of anthelmintic efficiency have been proposed, based on worm counts and microscopical examinations (Darling and Smillie, 3); but by far the most important measure of efficiency for field work, where the objective is the maximum reduction of human infestation and soil pollution in the minimum time, is the average percentage of all hookworms present removed by first treatment, as determined by subsequent "test treatment" of 3 c.c. of oil of chenopodium. Many recent workers have taken the percentage of 'cures,' as determined by microscopic re-examination, as a measure of equal value (Sawyer, et al., 14), and others (D'Estefano, 4) consider it the only valid measure of efficiency.

Total anthelmintic efficiency will depend upon individual efficiencies for male and female *Necator* and male and female *Ancylostoma* and the incidence of each of these forms in the total worm population. As noted above, *Ancylostoma* is more resistant to anthelmintics than is *Necator*. Females of both species are more resistant than are males of the same species to the action of chenopodium (Darling, et al., 1) On the contrary, the female *Necator* is less resistant than is the male *Necator* to carbon tetrachloride (Smillie and Pessoa, 17). Sawyer (15) failed to find such selectivity for this drug with *Ancylostoma*. In the use of maximum doses, the study of individual species and sex selectivity is relatively unimportant, as such selectivity tends to disappear as the dose of anthelmintic is increased (Darling, et al., 1). But where it is desired to employ the minimum dose for effective

results, a careful study should be made of such selective action of the drugs employed, as well as the species character of the worm population.

Although interesting and important to know the percentage efficiency of subsequent treatments with the same anthelmintic, the first treatment efficiency rate is the important factor to be considered in the choice of anthelmintic for field work today. With the development of more effective methods of treatment, the so-called "mass treatment" method has been widely adopted, and second and subsequent treatments, always more difficult to administer than first treatments, have rapidly diminished. The International Health Board (6), in cooperation with various governmental agencies, administered during the year 1923 717,191 first treatments and but 269,806 or 37.6 per cent. second treatments. The importance of first treatment efficiency is clear.

However, it must be remembered that the character as well as the degree of infestation may be altered by previous treatments with anthelmintics of species and sex selectivity, and probably with all anthelmintics, through removal on first treatment of immature and non-resistant individuals. Smillie found that "worms resistant to first treatment are resistant to the second also" (using a mixture of carbon tetrachloride and oil of chenopodium). It has recently been suggested (Soper, 19) that the *Necator/Ancylostoma* ratio of a geographical area may be altered through campaigns of selective medication. Thus it may be found advantageous to use a different anthelmintic for follow up campaigns from that used in the preliminary campaign.

Polyparasitism, especially where *Ascaris lumbricoides* is the offending organism, is an important problem in field work. The expulsion of Ascaris in quantity is a visual demonstration of anthelmintic efficiency of great popular appeal and not to be ignored. Lambert (7) attributes fatalities in children, treated with carbon tetrachloride, to *Ascaris* intoxication and reports that no cases have occurred after combining an ascaricide with this anthelmintic.

Extensive use of an anthelmintic in field work has proved a more delicate test of toxicity for the human host than has the study of controlled groups, which of necessity are small. Lambert treated over forty thousand cases before encountering a fatal case of intoxication with carbon tetrachloride. A wider margin of safety must be allowed for field work than for private or hospital practice.

Oil of chenopodium is particularly toxic for children under nine years of age and should not be administered to severe heart and kidney

cases, nor to menstruating or pregnant women. Well-nourished individuals seem to resist intoxication better than do undernourished ones. A high carbohydrate diet protects against intoxication with oil of chenopodium *in human subjects* (Salant, 13, Molloy, 12). A similar protective influence against liver destruction is exerted by the administration of a high carbohydrate diet to dogs for several days preceding the administration of carbon tetrachloride. (Davis, 3A.) Fats and alcohol when given with carbon tetrachloride greatly increase its toxicity for dogs (Lamson 9).

Hall (5), taking advantage of the work of Macht and Finesilver (11), who demonstrated that the simultaneous administration of a concentrated solution of magnesium sulphate with many drugs causes a reduction in the amount of such drugs absorbed into the blood from the intestine, administered simultaneously carbon tetrachloride and magnesium sulphate to dogs without any apparent reduction in the anthelmintic action of this drug. Lambert (8) adopted this method for field work and reports decreased toxicity with no decrease in anthelmintic efficiency. Soper (18)* showed by worm counts that the simultaneous administration of a concentrated solution of magnesium sulphate with a mixture of carbon tetrachloride and oil of chenopodium caused no reduction in efficiency, but a marked delay in the time of expulsion of worms.

The simultaneous administration of the purge should not only reduce the toxicity of the anthelmintic, but should markedly increase the number of treatments which can be given by a force in the field.

Any attempt to establish systematic therapeutic measures for hookworm disease must be based on drugs of known standard anthelmintic action and toxicity. Carbon tetrachloride is a simple chemical product, easily purified and relatively cheap. Oil of chenopodium, purchased by the International Health Board, is now being sent to the field with a statement of the ascaridol content of the particular lot shipped. That purchased during 1925 ranged from 68.5 to 78.7 per cent. in ascaridol.

Scope of the present paper.

The object of the experiments on which the present report is based was the determination of the optimum safe dose and method of administration of carbon tetrachloride, oil of chenopodium or a combination of carbon tetrachloride and oil of chenopodium, for field work in the Republic of Paraguay. It is hoped that the presentation

* Based on Groups 1 and 2 of the present series.

of the original data and the analysis of the efficiency rates are such that the findings may be of value in any geographical area *where the character and degree of hookworm infestation is known.*

This report is limited to the following points:

Degree and character of Paraguayan helminthological infestation;
Comparison of experimental species and sex efficiencies, as influenced by choice of anthelmintic, dosage and method of administration;
Comparison of Willis' flotation, Stoll's egg-count, and Darling's worm-count methods, as measures of anthelmintic efficiency;
Discussion of toxicity in controlled groups and in field campaign.

Collection of data, methods and material.

The work on which this report is based was carried out between March 1 and September 1, 1924, at Asunción, capital of the inland republic of Paraguay.*

Trial and test treatments, with worm counts for periods of forty-eight hours after each treatment, were administered to four hundred and nineteen individuals, divided into twenty-eight groups of from eight to twenty individuals per group. (Trial treatments were administered to four hundred and forty-one persons, but twenty-one of these were eliminated by desertion or discharge from institutions where the work was being done. One case was thrown out because of vomiting shortly after trial treatment.)

The individuals treated were distributed as follows:

Seventy-six policemen of Asunción, assigned to police duty from the National Army which is recruited from all parts of the republic;
Seventy-four prisoners of the Paraguayan penitentiary, located at Asunción (also recruited from all parts of the republic);
Sixty-five boys and two hundred and four girls in the National Asylum, Nuestra Señora de la Asunción.

A total of 82,856 hookworms were counted and classified as to species, sex and day of removal.

Preliminary Willis flotation examinations and Stoll egg-counts (20) were made on all cases. Second Willis examinations and Stoll counts were completed on one hundred and fifty cases fifteen days after trial treatments.

* This work has been possible only through the whole-hearted cooperation of the following colleagues and authorities: Drs. Eduardo Alvarim Romero and Rogelio Alvarez Bruguez, Médicos de Policía; Dr. J. Teodoro Decoud, Médico del Asylo; Chiefs of Police, Don Reinaldo Bibolini and Don Juan Vicente Ramirez; Felipe Viñales, Warden of the Penitentiary; and Sister Rafaela, Mother Superior of the Asylo de Nuestra Señora de la Asuncion.

TABLE I.

Trial treatment schedule.

Where.	Group No.	Cases.	No. in group.	Completed cases.	Adult dose (c.c.).			Modification.
					CCl_4.	Chenopodium.	Ascaridol.	
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*
Police Hospital.....	1	1–20	20	20	1.8	0.6	—	D
	2	21–40	20	20	1.8	0.6	—	S
	3	41–60	20	19	1.8	1.0	—	S
	4	61–80	20	17	1.0	1.0	—	S
Penitentiary.....	5	81–90	10	9	1.5	—	—	S
	6	91–100	10	8	1.0	—	—	S
	7	101–110	10	10	0.75	—	—	S
	8	111–120	10	9	1.25	—	—	S
	9	121–130	10	9	0.50	—	—	S
	10	131–140	10	10	1.8	—	—	S
	11	141–150	10	9	1.0	0.5	—	S
	12	151–160	10	10	1.6	0.8	—	S
Orphan Asylum.....	13	201–210 221–230	20	19	1.0	0.5	—	DD
	14	211–220	10	10	1.0	0.5	—	S
	15	231–240	10	9	1.0	0.5	—	SS
	16	241–250 261–270	20	20	1.6	0.8	—	SS
	17	251–260 271–280	20	19	1.6	0.8	—	DD
	18	281–300	20	20	1.5	—	—	S
	19	301–320	20	20	1.5	—	—	SR
	20	321–340	20	20	1.0	—	—	S
	21	341–360	20	19	2.4	—	—	S
	22	361–380	20	20	—	1.5	—	DD
	23	381–400	20	18	—	1.5	—	S
	24	401–410	10	8	—	—	0.75	S
	25	411–420	10	10	—	—	0.75	SS
	26	421–440	20	19	1.28	—	0.32	S
	27	441–460	20	20	1.6	—	0.40	S
	28	461–480	20	18	1.92	—	0.48	S

D = Delayed purge
DD = Divided dose and delayed purge
S = Simultaneous purge
SS = Simultaneous purge followed after 3 hours by 1 quart normal salt solution
SR = Simultaneous purge followed after 3 hours by magnesium sulphate in 25% solution

Trial treatments were given without previous preparation of the patients in any way. The first twenty policemen (Group 1) were selected by the writer as being anemic and probably infested with hookworm. The remaining three hundred and ninety-nine were treated without selection of any kind. Table I gives the schedule of trial treatments. All dosages are listed in cubic centimeters and were carefully measured with a 1 c.c. pipette, graduated in tenths of a cubic centimeter. Where two drugs are listed in Table I, as having been administered to the same group, they were given together in capsules freshly prepared the afternoon preceding treatment. Groups 1 to 12, inclusive, were adult men and received the adult dose as indicated. Groups 13 to 28, inclusive, were boys and girls in the asylum ranging from four to twenty-two years of age. These received one fifteenth of the indicated dose per year of age, up to the maximum dose, except Groups 22 and 23 which were treated with chenopodium alone and received one eighteenth of the adult dose per year of age, up to the maximum.

The carbon tetrachloride used was sold by the Eastman Kodak Co. as a chemically pure product. Analysis by Dr. Gustavo Crovato, C.E., gave the following results:

Density at 15° C.	1.603
Boiling point	78° C.
Non-volatile substances	absent
Hydrochloric acid	absent
Free chlorine	absent
Organic matter	traces
Aldehydes	absent
Phosgene	absent
Carbon bisulphide	absent

The oil of chenopodium used was from two lots (Parke, Davis Co.), the ascaridol content of one lot being 69.5, of the other lot 73.5 per cent.

The ascaridol was from the Burroughs-Wellcome Research Laboratories and guaranteed to contain over 90 per cent. of the active principle of oil of chenopodium.

Magnesium sulphate, in concentrated solution, with forty grams of the salt as an adult dose, was the purgative used in all cases. "Delayed purge" indicates one given two hours after an undivided dose of anthelmintic or one and one half hours after the last half of a divided dose. "Divided dose" indicates that the total dose indicated was divided into halves and administered with an interval of one hour. "Simultaneous purge" indicates a purge given simultaneously with the undivided dose of anthelmintic. "One quart salt solution" refers

to the administration of one quart of normal saline solution three hours after the pruge.

Test treatments were given after an interval of at least fifteen days. The test treatment (Darling and Smillie, 3) consisted of three cubic centimeters of oil of chenopodium, divided in three equal doses, administered at intervals of one hour, followed one and one half hours after the last dose by a purgative dose of magnesium sulphate in concentrated solution. Children were given one eighteenth of the adult dose per year of age up to the maximum. Test treatments were preceded by a preliminary purge, given on the eve of treatment.

Purgative doses of concentrated magnesium sulphate solution were administered to all patients twenty-four hours after both trial and test treatments to guarantee second day stools.

Stools were collected in numbered "jerries," and the first day's stool kept separate from the second. Carefully trained and reliable technicians washed the stools and removed the worms to individual glass containers bearing the number of the case, the date, and whether first or second day worms, in which they were preserved, after being prepared with hot alcohol and glycerine solution, until such time as the writer was able to make the counts and classify the specimens as to species and sex. Such worms, as were encountered partially digested, were not included in counts except when a definite diagnosis of sex and species could be made.

Degree and character of Paraguayan helminthological infestation.

The degree and character of hookworm infestation in the various groups studied is shown in Table II. The conditions found among the soldiers are probably representative of the infestation among young adults of the agricultural class throughout the country. Among the group of prisoners studied were political prisoners and others from the occupational groups not exposed to heavy infestation. The boys in the asylum are probably fairly representative of conditions among the children of the poorer class, as most of them are truly orphans, remain a shorter length of time than do the girls, and do not enjoy the same high standard of living conditions as do the girls. The girls of the asylum are in no way representative of any large class in the country. But a small percentage of them are truly orphans, the majority being pay boarders, whose fathers, because of absence from the capital or family reasons, are supporting them in the institution. A collateral study has revealed the fact that there is an increase in

TABLE II.

Degree and character of hookworm infestation in special Paraguayan groups.

Class.	No. of cases.	Harboring *Necator*.			Harboring *Ancylostoma*.			Total average.	*N./A.* ratio.	Maximum *Necator*.	Maximum *Ancylostoma*.	Maximum total.
		Cases.	Per cent.	Average.	Cases.	Per cent.	Average.					
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*
Soldiers	76	76	100	489.1	75	98.7	40.3	529.4	12.1	1.623	112	1.657
Prisoners	74	74	100	293.7	69	93.2	18.6	312.3	15.8	1.251	104	1.279
Asylum boys	65	65	100	135.5	56	86.2	6.6	142.1	20.5	606	46	619
Asylum girls	204	196	96.1	46.8	128	62.7	3.6	50.4	13.0	394	38	396
Total	419	411	98.1	184.4	328	78.3	13.4	197.7	13.8	1.623	112	1.657

the number of hookworms harbored among the boys with an increase in age, but that such expected increase among girls has been eliminated by the protective influence of asylum life.

Table II is a striking illustration of the failure of the percentage positives in a group to adequately indicate the gravity of infestation in that group.

Although 1,657 hookworms is a low maximum for a group harboring an average of over 500 worms, it must be remembered that all individuals in the heavier infested groups were soldiers on active duty, and that all recruits with severe anemia are rejected for military service.

The *Necator/Ancylostoma* ratio is much lower than was anticipated. In Porto Rico, where the ethnic stocks are Spanish, Negro and Amerind, no *Ancylostoma duodenale* occurs (Darling, 2),* and in Brazil, among natives of Portuguese, Negro and Indian descent, the *Necator/Ancylostoma* ratio is more than five times as great (Darling and Smillie, 5). The ethnic stocks of Paraguay are Spanish and Amerind. The occasional traces of negro descent, that are noted in the population, are said to have had their origin in the Brazilian occupation following the Paraguayan War, as there was never any important importation of negro slaves.

Local authorities claim that hookworm disease did not exist in Paraguay before the Brazilian occupation. If it be true that hookworm disease in Paraguay is entirely due to post-war infestation, the only possible explanation of present findings is that Paraguayan conditions are so much more favorable to the spread of *Ancylostoma duodenale* than to the dissemination of *Necator americanus*, that the *Necator/Ancylostoma* ratio has been greatly altered since the supposed original infection sixty years ago.

That hookworm disease was not entirely absent from Paraguay in early colonial days is indicated by the occurrence of the word 'py-seboí' in the Guarani (Indian)-Spanish dictionary prepared by Antonio Ruiz de Montoya, a Jesuit priest, and published in 1639 A.D., one hundred and four years after the founding of Asunción by the Spaniards. Montoya translates "py-seboí" as "itching or irritation of the feet," and the word is currently used today to designate "ground-itch." Strangely enough, the analysis of the compound word, "py-seboí," ("py"—foot, "seboí"—worm) suggests that the aborigines had an inkling of biological facts not established by helminthologists until some centuries later.

* The finding of *Ancylostoma duodenale* in Porto Rico has recently been reported. (Hill, R. B., "The Hookworm Campaign in Porto Rico, 1923," I. H. B. Bulletin, Vol. 4, No. 4, April 1924.

The probable explanation of the character of hookworm infestation encountered today is that there has existed in Paraguay an infestation with *Ancylostoma* since early Spanish colonial days, and that on this has been superimposed a Brazilian infestation, largely of *Necator*.

Although the *Necator* problem is of the greatest importance in Paraguay, there is a sufficiently high *Ancylostoma* infestation to justify its consideration in the selection of the anthelmintic for field work.

Ascaris lumbricoides was diagnosed by the Willis examination in 36 cases (8.6 per cent.). Only 8 of these 36 cases yielded *Ascaris* after trial treatment and one after test treatment. Thirteen cases, missed by the microscope, yielded *Ascaris* on treatment, five of which had only male worms. Only two Ascarids were eliminated by the test treatment of 3 c.c. of oil of chenopodium. Of forty-nine cases, or 11.7 per cent., shown by microscopic examination or worm count to harbor *Ascaris*, only sixteen passed worms in the forty-eight-hour period following treatment. Since all cases were treated with maximum doses of chenopodium, known to be very effective against *Ascaris*, there must have been a delayed expulsion of *Ascaris* beyond the period of observation.

Trichuris trichiura eggs were found in 182 cases (43.4 per cent.). Only thirty *Trichuris* adults were recovered in forty-eight-hour collections, sixteen after trial treatment and fourteen after test treatment. That there may be a sex selective action with the drugs used, is suggested by the fact that ten of sixteen worms removed by combination of carbon tetrachloride and oil of chenopodium were males and eleven of fourteen removed by oil of chenopodium alone were males.

Oxyuris was diagnosed by worm counts in the majority of cases. The following percentages of infested cases were found in the various groups:

Class.	Trial treatment.	Test treatment.	Maximum *Oxyuris* per case.	
			Trial.	Test.
Soldiers	5.3	1.3	3	1
Prisoners	24.3	10.8	14	1
Boys' Asylum	33.8	10.8	17	13
Girls' Asylum	48.5	14.5	191	50
Total	34.1	12.7	191	50

Taenia was diagnosed in 15 cases (3.1 per cent.).

The infestation rates for *Ascaris* and *Trichuris* are approximately 100 per cent. higher in this small series of cases than have been found for routine field examinations. Eleven thousand routine examinations gave *Ascaris* a rate of 5.3 and *Trichuris* a rate of 22.4 per cent.

Comparison of experimental species and sex efficiencies as influenced by choice of anthelmintic, dosage and method of administration.

The number of percentage of hookworms expelled by each group, in the forty-eight hour periods after trial and test treatments, distributed by species and sex are shown in Table III. Details of the manner of treating each group will be found in Table I. Results by individual cases are given in the twenty-eight tables of the Appendix (Table *A* to *AB* inclusive.)*

Darling, et al. (1), working in areas where both *Necator americanus* and *Ancylostoma duodenale* are found, and administering thymol and oil of chenopodium, showed that there is a difference in resistance to anthelmintic action which apparently depends upon the size of the form, as the decreasing order of resistance found is, female *Ancylostoma*, male *Ancylostoma*, female *Necator*, male *Necator*. They recognized the importance of treating the worm rather than the host. To quote, "The distribution and relative numbers of *Ancylostoma duodenale* are important on account of their relation to effective and economical treatment. For, since there is a definite relation between dosage of drug and respective species of worm (more drug being required to dislodge the more resistant *Ancylostoma duodenale*), it is highly desirable to know the *Ancylostoma* formula of the people who are being treated. If this is known, it is comparatively simple to adjust the dosage of the drug efficiently and economically according to the species of worms which are to be removed."

Smillie and Pessoa, (17) working with carbon tetrachloride in a region where *Necator* predominates, reported a greater resistance of males than of females to this drug. Sawyer et al. (14), using relatively high doses of carbon tetrachloride, were unable to confirm this finding for *Ancylostoma*, but noted that ancylostomas are more resistant than are necators. Thus the question arises, whether the differences noted with chenopodium are really due to size alone, or whether there is not a species and sex selectivity of anthelmintic action which varies with

* These tables have been omitted from publication at this place, as they were too lengthy; they are on file with the librarian of the Rockefeller Foundation, 61 Broadway, New York City, and can be consulted on application.

TABLE III.

Distribution of worms expelled by trial and test treatments by sex and species.

Group No.	Cases.	*Necator.* Female. No. expelled. Trial treatment.	Test treatment.	Total.	Per cent. expelled trial treatment.	Male. No. expelled. Trial treatment.	Test treatment.	Total.	Per cent. expelled trial treatment.	*Ancylostoma.* Female. No. expelled. Trial treatment.	Test treatment.	Total.	Per cent. expelled trial treatment.	Male. No. expelled. Trial treatment.	Test treatment.	Total.	Per cent. expelled trial treatment.	Total. Trial treatment.	Test treatment.	Total.	Per cent. expelled trial treatment.	Worms expelled. *Necator.*	*Ancylostoma.*	Female.	Male.	Per cent. expelled; trial treatment. *Necator.*	*Ancylostoma.*	Female.	Male.	
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*P*	*Q*	*R*	*S*	*P*	*U*	*V*	*W*	*X*	*Y*	*Z*	A_1	B_1	C_1	D_1	E_1
1	1–20	4284	33	4317	99.2	5243	93	5336	98.3	412	153	565	72.9	328	72	400	82.0	10267	351	10618	96.7	9653	965	4882	5736	98.7	76.7	96.2	97.1	17.5
2	21–40	4673	26	4699	99.4	4874	131	5005	97.4	390	153	543	71.8	274	80	354	77.4	10211	390	10601	96.3	9704	897	5242	5359	98.4	74.0	96.6	96.1	19.5
3	41–60	5485	10	5495	99.8	4761	31	4792	99.4	313	59	372	84.2	246	16	262	93.9	10805	116	10921	98.9	10287	634	5867	5054	99.6	88.2	98.8	99.1	6.1
4	61–80	4007	56	4063	98.6	3250	217	3467	93.7	216	105	321	67.3	208	38	246	84.6	7681	416	8097	94.9	7580	567	4384	3713	96.4	74.8	96.3	93.1	24.5
5	81–90	1392	51	1443	96.5	1126	121	1247	90.3	21	47	68	30.9	14	42	56	25.0	2553	261	2814	90.7	2690	124	1511	1303	93.6	28.2	93.5	87.5	29.0
6	91–100	922	46	968	95.2	875	120	995	87.9	28	57	85	32.9	27	70	97	27.8	1852	293	2145	86.3	1963	182	1053	1092	91.5	30.2	90.2	82.6	36.6
7	101–110	1279	247	1526	83.8	1005	507	1512	66.5	28	147	175	16.0	12	145	157	7.6	2324	1046	3370	69.0	3038	332	1701	1669	75.2	12.0	76.8	60.9	104.6
8	111–120	999	55	1054	94.8	833	213	1046	79.6	15	48	63	23.8	16	47	63	25.4	1863	363	2226	83.7	2100	126	1117	1109	87.2	24.6	90.8	76.6	40.3
9	121–130	1369	354	1723	79.5	918	704	1622	56.6	5	68	73	6.8	4	100	104	3.8	2296	1226	3522	65.2	3345	177	1796	1726	88.4	5.1	76.5	53.4	136.2
10	131–140	1596	125	1721	92.7	1074	329	1403	76.6	20	60	80	25.2	17	31	48	35.4	2707	545	3252	83.2	3124	128	1801	1451	85.5	28.9	89.7	75.2	54.5
11	141–150	1893	9	1902	99.5	1676	106	1782	94.1	39	79	118	33.1	68	34	102	66.7	3676	228	3904	94.2	3684	220	2020	1884	96.9	48.6	95.6	92.6	25.3
12	151–160	959	0	959	100	825	4	829	99.5	25	10	35	71.4	44	6	50	88.0	1853	20	1873	98.9	1788	85	994	879	99.8	81.2	99.0	98.9	2.0
13	201–210 / 221–230	243	9	252	96.4	295	15	310	95.2	32	22	54	59.3	28	6	34	82.4	598	52	650	92.0	562	88	306	344	95.7	68.2	89.9	93.9	2.7
14	211–220	313	0	313	100	339	0	339	100	14	4	18	77.8	11	0	11	100	677	4	681	99.4	652	29	331	350	100	86.2	98.8	100	0.4
15	231–240	180	1	181	99.4	274	12	286	95.8	12	6	18	66.7	7	3	10	70.0	473	22	495	95.6	467	28	199	296	97.2	67.9	96.5	94.9	2.4
16	241–250 / 261–270	555	0	555	100	523	7	530	98.7	63	18	81	77.8	41	2	43	95.3	1182	27	1209	97.8	1085	124	636	573	99.4	83.9	97.2	98.4	1.4
17	251–260 / 271–280	526	4	530	99.2	429	36	465	92.3	21	6	27	77.8	12	1	13	92.3	988	47	1035	95.5	995	40	557	478	96.2	82.5	98.2	92.3	2.4
18	281–300	724	7	731	99.0	760	54	814	93.4	32	23	55	58.2	25	21	46	54.3	1541	105	1646	93.6	1545	101	788	860	96.1	56.4	96.2	91.3	5.2
19	301–320	489	7	496	98.6	369	59	428	86.2	16	16	32	50.0	17	16	33	51.5	891	98	989	90.1	924	65	528	461	92.9	50.8	95.6	83.7	4.9
20	321–340	187	9	196	95.4	181	38	219	82.6	13	11	24	54.2	10	16	26	38.5	391	74	465	84.1	415	50	220	245	88.7	46.0	90.9	78.0	3.7
21	341–360	547	7	554	98.7	540	15	555	97.3	46	24	70	65.7	25	19	44	56.8	1158	65	1223	94.7	1109	114	624	599	98.0	62.3	95.0	94.3	3.4
22	361–380	184	11	195	94.4	157	11	168	93.5	19	10	29	65.5	10	4	14	71.4	370	36	406	91.1	363	43	224	182	93.9	67.4	90.6	91.8	1.8
23	381–400	451	73	524	86.1	464	35	499	93.0	4	11	15	26.7	9	7	16	56.2	928	126	1054	88.0	1023	31	539	515	89.4	41.9	84.4	91.8	7.0
24	401–410	130	14	144	90.3	131	10	141	92.9	3	5	8	37.5	5	1	6	83.3	269	30	299	90.0	285	14	152	147	91.6	57.1	87.5	92.5	3.7
25	411–420	431	121	552	78.1	417	128	545	76.5	1	9	10	10.0	6	13	19	31.6	855	271	1126	75.9	1097	29	562	564	77.3	24.1	76.9	75.0	27.1
26	421–440	1073	14	1087	98.7	958	106	1064	90.0	20	30	50	40.0	22	17	39	56.4	2073	167	2240	92.5	2151	89	1137	1103	94.4	47.2	96.1	88.8	8.8
27	441–460	1165	5	1170	99.6	1063	23	1086	97.9	68	30	98	69.4	91	6	97	93.8	2387	64	4251	97.4	2256	195	1268	1183	98.8	81.5	97.2	97.5	3.2
28	461–480	1648	2	1650	99.9	1755	20	1775	98.9	52	18	70	74.3	46	3	49	93.9	3501	43	3544	98.8	3425	119	1720	1824	99.4	82.4	98.8	98.7	2.4
Total		37704	1296	39000	96.7	35115	3145	38260	91.8	1928	1229	3157	61.1	1623	816	2439	60.5	76370	6486	82856	92.2	77290	5596	42157	40699	94.3	63.5	94.0	90.3	15.5

the drug employed. Smillie accepted the latter explanation, and having discovered that carbon tetrachloride and oil of chenopodium have complementary action on the hookworm, but independent action on the host, was the first to suggest a combination of the two drugs.

Since carbon tetrachloride and oil of chenopodium have both been reported to possess a differential species and sex efficiency, it is essential to consider the question of their combination for field work as a four-fold problem. The data presented have, therefore, been analyzed as to efficiency against female *Necator*, male *Necator*, female *Ancylostoma* and male *Ancylostoma*.

In order to answer the question, "What per cent. efficiency has a given method against all hookworms under Paraguayan conditions?" the total efficiency was also calculated. Finding, however, that the percentage of males and females and the *Necator/Ancylostoma* ratio varied in different groups, a standard Paraguayan worm population was set up from the data in Table IV, and the corrected Paraguayan

TABLE IV.

Percentage distribution of Paraguayan hookworms by sex and species.

Class.	Average number of hookworms.	Per cent. of total worms.				Per cent. of *Necator*.		Per cent. of *Ancylostoma*.		Per cent. of total worms.	
		Necator.		*Ancylostoma*.		F.	M.	F.	M.	*Necator*.	*Ancylostoma*.
		F.	M.	F.	M.						
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*
Soldiers	529.3	46.2	46.2	4.5	3.1	50	50	58.8	41.2	92.4	7.6
Prisoners	312.2	48.9	45.2	3.0	2.9	52	48	50.7	49.3	94.1	5.9
Orphans:											
Boys	142.1	47.0	47.0	3.4	2.6	50	50	56.7	43.3	94.0	6.0
Girls	47.5										
Total	196.8	47.1	46.2	3.8	2.9	50.5	49.5	56.4	43.6	93.3	6.7

efficiency rates calculated for this standard population. Table V shows the method used in this calculation. Column *P* is the product of column *G* times .471, which represents the female *Necator* element of the standard population (Table IV). The formation of columns *Q*, *R*, *S*, is similar. Column *T* is the summation of items in columns *P*, *Q*, *R*, and *S*. Column *U* gives the difference between the crude

TABLE V.

Correction of group efficiency rates for standard Paraguayan worm population.

Group No.	Drug.	Adult dose.	Purge.	Average total worms.	Average worms test treatment.	Per cent. efficiency total worms of group.									Corrected efficiency for standard Paraguayan worm population.					
						Necator.			*Ancylostoma.*			All hookworms.			% EN x .471	% MN x .462	% EA x .038	% MA x .029	Total corrected rate.	Difference $T-O$.
						F.	M.	T.	F.	M.	T.	F.	M.	T.						
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*P*	*Q*	*R*	*S*	*T*	*U*
1	(3 x 1)M_1	2.4	D	530.9	17.5	99.2	98.3	98.7	72.9	82.0	76.7	96.2	97.1	96.7	46.7	45.4	2.8	2.4	97.3	+0.6
2	(3 x 1)M_1	2.4	S	530.0	19.5	99.4	97.4	98.4	71.8	77.4	74.0	96.6	96.1	96.3	46.8	45.0	2.7	2.2	96.8	+0.5
3	(9 x 5)M_1	2.8	S	574.8	6.1	99.8	99.4	99.6	84.2	93.9	88.2	98.8	99.1	98.9	47.0	45.9	3.2	2.7	98.9	0.0
4	(1 x 1)M_1	2.0	S	476.3	24.5	98.6	93.7	96.4	67.3	84.6	74.8	96.3	93.1	94.9	46.4	43.3	2.6	2.4	94.7	−0.2
5	CCl_4	1.5	S	312.7	29.0	96.5	90.3	93.6	30.9	25.0	28.2	93.5	87.5	90.7	45.4	41.7	1.2	0.7	89.1	−1.6
6	CCl_4	1.0	S	268.1	36.6	95.2	87.9	91.5	32.9	27.8	30.2	90.2	82.6	86.3	44.8	40.6	1.2	0.8	87.5	+1.2
7	CCl_4	0.75	S	337.0	104.6	83.8	66.5	75.2	16.0	7.6	12.0	76.8	60.9	69.0	39.5	30.7	0.6	0.2	71.0	+2.0
8	CCl_4	1.25	S	247.3	40.3	94.8	79.6	87.2	23.8	25.4	24.6	90.8	76.6	83.7	44.6	36.8	0.9	0.7	83.1	−0.6
9	CCl_4	0.50	S	391.3	136.2	79.5	56.6	68.4	6.8	3.8	5.1	76.5	53.4	65.2	37.4	26.1	0.3	0.1	64.0	−1.2
10	CCl_4	1.8	S	325.2	54.5	92.7	76.6	85.5	25.0	35.4	28.9	89.7	75.2	83.2	43.7	35.4	0.9	1.0	81.0	−2.2
11	(2 x 1)M_1	1.5	S	433.8	25.3	99.5	94.1	96.9	33.1	66.7	48.6	95.6	92.6	94.2	46.9	43.5	1.3	1.9	93.5	−0.7
12	(2 x 1)M_1	2.4	S	187.3	2.0	100.0	99.5	99.8	71.4	88.0	81.2	99.0	98.9	98.9	47.1	46.0	2.7	2.5	98.3	−0.6
13	(2 x 1)M_1	1.5	DD	34.2	2.7	96.4	95.2	95.7	59.3	82.4	68.2	89.9	93.9	92.0	45.4	44.0	2.2	2.4	94.0	+2.0
14	(2 x 1)M_1	1.5	S	68.1	0.4	100.0	100.0	100.0	77.8	100.0	86.2	98.8	100.0	99.4	47.1	46.2	3.0	2.9	99.2	−0.2
15	(2 x 1)M_1	1.5	SS	55.0	2.4	99.4	95.8	97.2	66.7	70.0	67.9	96.5	94.9	95.5	46.8	44.3	2.5	2.0	95.6	+0.1
16	(2 x 1)M_1	2.4	SS	60.5	1.4	100.0	98.7	99.4	77.8	95.3	83.9	97.2	98.4	97.8	47.1	45.6	3.0	2.8	98.4	+0.6
17	(2 x 1)M_1	2.4	DD	54.5	2.5	99.2	92.3	96.0	77.8	92.3	82.5	98.2	92.3	95.5	46.7	42.6	3.0	2.7	95.0	−0.5

TABLE V.—(*Continued*)

Group No.	Drug.	Adult dose.	Purge.	Average total worms.	Average worms test treatment.	Per cent. efficiency total worms of group.									Corrected efficiency for standard Paraguayan worm population.					
						Necator.			*Ancylostoma.*			All hookworms.			% FN x .471	% MN x .662	% FA x .038	% MA x .029	Total corrected rate.	Difference $T - O$
						F.	M.	T.	F.	M.	T.	F.	M.	T.						
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*P*	*Q*	*R*	*S*	*T*	*U*
18	CCl_4	1.5	S	82.3	5.2	99.0	93.4	96.1	58.2	54.3	56.4	96.2	91.3	93.6	46.6	43.1	2.2	1.6	93.6	0.0
19	CCl_4	1.5	SR	49.5	4.9	98.6	86.2	92.9	50.0	51.5	50.8	95.6	83.7	90.1	46.4	39.9	1.9	1.5	89.7	−0.4
20	CCl_4	1.0	S	23.3	3.7	95.4	82.6	88.7	54.2	38.5	46.0	90.9	78.0	84.1	44.9	38.2	2.1	1.1	86.3	+2.2
21	CCl_4	2.4	S	64.4	3.4	98.7	97.3	98.0	65.7	56.8	62.3	95.0	94.3	94.7	46.5	45.0	2.5	1.6	95.6	−0.9
22	Chen.	1.5	DD	20.3	1.8	94.4	93.5	93.9	65.5	71.4	67.4	90.6	91.8	91.1	44.5	43.2	2.5	2.1	92.2	+1.1
23	Chen.	1.5	S	58.7	7.0	86.1	93.0	89.4	26.7	56.2	41.9	84.4	91.8	88.0	40.5	43.0	1.0	1.6	86.2	−1.8
24	Asc.	0.75	S	37.4	3.7	90.3	92.9	91.6	37.5	83.3	57.1	87.5	92.5	90.0	42.5	43.0	1.4	2.4	89.3	−0.7
25	Asc.	0.75	SS	112.6	27.6	78.1	76.5	77.3	10.0	31.6	24.1	76.9	75.0	75.9	36.8	35.3	0.4	0.9	73.4	−2.5
26	(4 x 1)M_2	1.6	S	117.9	8.8	98.7	90.0	94.4	40.0	56.4	47.2	96.1	88.8	92.5	46.5	41.6	1.5	1.6	91.2	−1.3
27	(4 x 1)M_2	2.0	S	122.6	3.2	99.6	97.9	98.8	69.4	93.8	81.5	97.2	97.5	97.4	46.9	45.2	2.6	2.7	97.5	+0.1
28	(4 x 1)M_2	2.4	S	196.9	2.4	99.9	98.9	99.4	74.3	93.9	82.4	98.8	98.7	98.8	47.0	45.7	2.8	2.7	98.3	−0.5

D = Delayed purge.
DD = Divided dose and delayed purge.
S = Simultaneous purge.
SS = Simultaneous purge followed after 3 hours by a quart of normal salt solution.
SR = Simultaneous purge followed after 3 hours by magnesium sulphate in 25% solution.
M_1 = Carbon tetrachloride and oil of chenopodium.
M_2 = Carbon tetrachloride and ascaridol.

TABLE VI.

Correction of group Necator and Ancylostoma efficiency rates for 50 per cent. females.

Group No.	Drug.	Adult dose.	Purge.	Corrected efficiency Paraguay Table III.	Corrected species efficiency for 50% females.						Uncorrected.	
					Necator.			*Ancylostoma.*			*Necator.*	*Ancylostoma.*
					F.	M.	Corrected total.	F.	M.	Corrected total.		
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*
14	(2 x 1)M_1	1.5	S	99.2	100.0	100.0	100.0	77.8	100.0	88.9	100.0	86.2
3	(9 x 5)M_1	2.8	S	98.9	99.8	99.4	99.6	84.2	93.9	89.0	99.6	88.2
16	(2 x 1)M_1	2.4	SS	98.4	100.0	98.7	99.3	77.8	95.3	86.5	99.4	83.9
12	(2 x 1)M_1	2.4	S	98.3	100.0	99.5	99.7	71.4	88.0	79.7	99.8	81.2
28	(4 x 1)M_2	2.4	S	98.3	99.9	98.9	99.4	74.3	93.9	84.1	99.4	82.4
27	(4 x 1)M_2	2.0	S	97.5	99.6	97.9	98.7	69.4	93.8	81.6	98.8	81.5
1	(3 x 1)M_1	2.4	D	97.3	99.2	98.3	98.7	72.9	82.0	77.4	98.7	76.7
2	(3 x 1)M_1	2.4	S	96.8	99.4	97.4	98.4	71.8	77.4	74.6	98.4	74.0
15	(2 x 1)M_1	1.5	SS	95.6	99.4	95.8	97.6	66.7	70.0	68.3	97.2	67.9
21	CCl_4	2.4	S	95.6	98.7	97.3	98.0	65.7	56.8	61.2	98.0	62.3
17	(2 x 1)M_1	2.4	DD	95.0	99.2	92.3	95.7	77.8	92.3	85.0	96.0	82.5
4	(1 x 1)M_1	2.0	S	94.7	98.6	93.7	96.1	67.3	84.6	75.9	96.4	74.8
13	(2 x 1)M_1	1.5	DD	94.0	96.4	95.2	95.8	59.3	82.4	70.8	95.7	68.2
18	CCl_4	1.5	S	93.6	99.0	93.4	96.2	58.2	54.3	56.2	96.1	56.4
11	(2 x 1)M_1	1.5	S	93.5	99.5	94.1	96.8	33.1	66.7	49.9	96.9	48.6
22	Chen.	1.5	DD	92.2	94.4	93.5	93.9	65.5	71.4	68.4	93.9	67.4
26	(4 x 1)M_2	1.6	S	91.2	98.7	90.0	94.3	40.0	56.4	48.2	94.4	47.2
19	CCl_4	1.5	SR	89.7	98.6	86.2	92.4	50.0	51.5	50.7	92.9	50.8
24	Ascar.	0.75	S	89.3	90.3	92.9	91.6	37.5	83.3	60.4	91.6	57.1
5	CCl_4	1.5	S	89.1	96.5	90.3	93.4	30.9	25.0	27.9	93.6	28.2
6	CCl_4	1.0	S	87.5	95.2	87.9	91.5	32.9	27.8	30.3	91.5	30.2
20	CCl_4	1.0	S	86.3	95.4	82.6	89.0	54.2	38.5	46.3	88.7	46.0
23	Chen.	1.5	S	86.2	86.1	93.0	89.5	26.7	56.2	41.4	89.4	41.9
8	CCl_4	1.25	S	83.1	94.8	79.6	87.2	23.8	25.4	24.6	87.2	24.6
10	CCl_4	1.8	S	81.0	92.7	76.6	84.6	25.0	35.4	30.2	85.5	28.9
25	Ascar.	0.75	SS	73.4	78.1	76.5	77.3	10.0	31.6	20.8	77.3	24.1
7	CCl_4	0.75	S	71.0	83.8	66.5	75.1	16.0	7.6	11.8	75.2	12.0
9	CCl_4	0.50	S	64.0	79.5	56.6	68.0	6.8	3.8	5.3	68.4	5.1

D = Delayed purge.
DD = Divided dose and delayed purge.
S = Simultaneous purge.
SS = Simultaneous purge followed after 3 hours by a quart of normal salt solution.
SR = Simultaneous purge followed after 3 hours by magnesium sulphate in 25% solution.
M_1 = Carbon tetrachloride and oil of chenopodium.
M_2 = Carbon tetrachloride and ascaridol.

TABLE VII.

Theoretical values for efficiency and toxicity compared with actual efficiency rates by species and sex.

Group No.	Drug.	Dose.	Purge.	Theoretical values. 3 c.c. CCl_4 = 100 1.5 c.c. Chen. = 100 1.1 c.c. Ascar. = 100		Per cent. experimental efficiency.					
						Necator.			*Ancylostoma.*		
				Efficiency.	Toxicity.	F.	M.	T.	F.	M.	T.
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*
9	CCl_4	.5	S	17	17	79.5	56.6	68.0	6.8	3.8	5.3
7	CCl_4	.75	S	25	25	83.8	66.5	75.1	16.0	7.6	11.8
6	CCl_4	1.0	S	33	33	95.2	87.9	91.5	32.9	27.8	30.3
20	CCl_4	1.0	S	33	33	95.4	82.6	89.0	54.2	38.5	46.3
8	CCl_4	1.25	S	42	42	94.8	79.6	87.2	23.8	25.4	24.6
5	CCl_4	1.5	S	50	50	96.5	90.3	93.4	30.9	25.0	27.9
18	CCl_4	1.5	S	50	50	99.0	93.4	96.2	58.2	54.3	56.2
19	CCl_4	1.5	SR	50	50	98.6	86.2	92.4	50.0	51.5	50.0
10	CCl_4	1.8	S	60	60	92.7	76.6	84.6	25.0	35.4	30.2
11	$(2 \times 1)M_1$	1.5	S	66.7	33	99.5	94.1	96.8	33.1	66.7	49.9
13	$(2 \times 1)M_1$	1.5	DD	66.7	33	96.4	95.2	95.8	59.3	82.4	70.8
14	$(2 \times 1)M_1$	1.5	S	66.7	33	100.0	100.0	100.0	77.8	100.0	88.9
15	$(2 \times 1)M_1$	1.5	SS	66.7	33	99.4	95.8	97.6	66.7	70.0	68.3
26	$(4 \times 1)M_2$	1.5	S	67.3	40	98.7	90.0	94.3	40.0	56.4	48.2
24	Ascar.	.75	S	68.2	68	90.3	92.9	91.6	37.5	83.3	60.4
25	Ascar.	.75	SS	68.2	68	78.1	76.5	77.3	10.0	31.6	20.8
21	CCl_4	2.4	S	80	80	98.7	97.3	98.0	65.7	56.8	61.2
27	$(4 \times 1)M_2$	2.0	S	90	53	99.6	97.9	98.7	69.4	93.8	81.6
22	Chen.	1.5	DD	100	100	94.4	93.5	94.0	65.5	71.4	68.4
23	Chen.	1.5	S	100	100	86.1	93.0	89.5	26.7	56.2	41.4
4	$(1 \times 1)M_1$	2.0	S	100	67	98.6	93.7	96.1	67.3	84.6	75.9
1	$(3 \times 1)M_1$	2.4	D	100	60	99.2	98.3	98.7	72.9	82.0	77.4
2	$(3 \times 1)M_1$	2.4	S	100	60	99.4	97.4	98.4	71.8	77.4	74.6
16	$(2 \times 1)M_1$	2.4	SS	106.7	53	100.0	98.7	99.3	77.8	95.3	86.5
17	$(2 \times 1)M_1$	2.4	DD	106.7	53	99.2	92.3	95.7	77.8	92.3	85.0
28	$(4 \times 1)M_2$	2.4	S	107.6	64	99.9	98.9	99.4	74.3	93.9	84.1
12	$(2 \times 1)M_1$	2.4	S	111	56	100.0	99.5	99.7	71.4	88.0	79.7
3	$(9 \times 5)M_1$	2.8	S	127	67	99.8	99.4	99.6	84.2	93.9	89.0

D = Delayed purge.
DD = Divided dose and delayed purge.
S = Simultaneous purge.
SS = Simultaneous purge followed after 3 hours by 1 quart of normal salt solution.
SR = Simultaneous purge followed after 3 hours by magnesium sulphate in 25% solution.
M_1 = Carbon tetrachloride and oil of chenopodium.
M_2 = Carbon tetrachloride and ascaridol.

TABLE VIII.

Theoretical values for efficiency and toxicity and actual efficiency rates by species and sex in groups given simultaneous purge compared with similar values for chenopodium in divided dose and with delayed purge.

Groups No.	Drug.	Adult dose.	Purge.	Theoretical values. 5 c.c. CCl_4 = 100 1.5 c.c. Chen. = 100 1.1 c.c. Ascar. = 100		Per cent. experimental efficiency.						Number of *Ancylostoma* in group.
						Necator.			*Ancylostoma.*			
				Efficiency.	Toxicity.	F.	M.	T.	F.	M.	T.	
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*
9	CCl_4	0.5	S	17	17	79.5	56.6	68.0	6.8	3.8	5.3	177
7	CCl_4	0.75	S	25	25	83.8	66.5	75.1	16.0	7.6	11.8	332
6 and 20	CCl_4	1.0	S	33	33	95.3	87.0	91.1	37.6	30.0	33.8	232
8	CCl_4	1.25	S	42	42	94.8	79.6	87.2	23.8	25.4	24.6	126
5 and 18	CCl_4	1.5	S	50	50	97.3	91.5	94.4	43.1	38.2	40.6	225
10	CCl_4	1.8	S	60	60	92.7	76.6	84.6	25.0	35.4	30.2	128
11 and 14	(2 x 1)M_1	1.5	S	66.7	33	99.6	95.0	97.3	39.0	70.0	54.5	249
26	(4 x 1)M_2	1.5	S	67.3	40	98.7	90.0	94.3	40.0	56.4	48.2	89
24	Ascar.	0.75	S	68.2	68	90.3	92.9	91.6	37.5	83.3	60.4	14
21	CCl_4	2.4	S	80	80	98.7	97.3	98.0	65.7	56.8	61.2	114
27	(4 x 1)M_2	2.0	S	90	53	99.6	97.9	98.7	69.4	93.8	81.6	195
22	Chen.	1.5	DD	100	100	94.4	93.5	93.9	65.5	71.4	68.4	43
4	(1 x 1)M_1	2.0	S	100	67	98.6	93.7	96.1	67.3	84.6	75.8	567
2	(3 x 1)M_1	2.4	S	100	60	99.4	97.4	98.4	71.8	77.4	74.6	897
12	(2 x 1)M_1	2.4	S	106.7	53	100.0	99.5	99.7	71.4	88.0	79.7	85
28	(4 x 1)M_2	2.4	S	107.6	64	99.9	98.9	99.5	74.3	93.9	84.1	119
3	(9 x 5)M_1	2.8	S	127	67	99.8	99.4	99.6	84.2	93.9	89.0	634

D = Delayed purge.
DD = Divided dose and delayed purge.
S = Simultaneous purge.
SS = Simultaneous purge followed after 3 hours by 1 quart of normal salt solution.
SR = Simultaneous purge followed after 3 hours by magnesium sulphate in 25% solution.
M_1 = Carbon tetrachloride and oil of chenopodium.
M_2 = Carbon tetrachloride and ascaridol.

efficiency rate of column *O* and the corrected rate of column *T*. In no group is such difference greater than 2.5 per cent., but this difference is sufficient to alter the precedence in total efficiency in some cases.

In calculating total *Necator* and total *Ancylostoma* efficiencies in Table VI, it has been assumed that the number of males equals the number of females in any large part of the population, although our figures show a marked excess of female *Ancylostoma* over males of the same species. The correction for fifty per cent. females in no group alters the *Necator* efficiency more than .9 per cent., but in two groups the *Ancylstoma* efficiency is altered by 3.3 per cent.

In further analysis of these data, the corrected rates will always be used, the corrected standard rate for Paraguay for both species together, and the rate corrected for fifty per cent. females for individual species. It can readily be seen from Table VI that column *E* does not give the true picture of anthelmintic efficiency. Separate considerations of columns *F*, *G*, *I*, and *J* are necessary to an understanding of the figures in column *E*.

Working on the assumption that the anthelmintic effects of carbon tetrachloride and oil of chenopodium, when given together, are complementary, but that their toxicities for the human host are not, a theoretical equal efficiency and toxicity value of 100 was assigned to adult doses of the three drugs used, 3 c.c. of carbon tetrachloride, 1.5 c.c. oil of chenopodium and 1.1 c.c. ascaridol. Table VII presents the species and sex efficiencies of the twenty-eight groups, arranged in the order of increasing theoretical efficiency. Theoretical toxicity, equalling the greatest toxicity value of either drug in a combined treatment, is given in column F. For more careful analysis and to eliminate the possible effects of other modifications (see Table X) Table VIII was formed for the comparison of anthelmintic efficiencies by sex and species of the different dosages which were employed with simultaneous purge, with the anthelmintic efficiency of the standard field treatment of oil of chenopodium (1.5 c.c. in divided dose and with delayed purge of magnesium sulphate). All percentages based on *Necator* in Table VIII are from large enough groups to reduce to a minimum variations due to errors in sampling. The same is not true in all groups in regard to Ancylostoma. That the reader may have before him the number of *Ancylostoma* in each group on which percentages are based, such information has been repeated in column *M*.

The data from columns *E*, *G*, *H*, *J*, and *K* are plotted in Fig. 1.

Figure 1 shows that carbon tetrachloride possesses a definite sex selectivity. This selectivity is much greater in the case of *Necator* than in the case of *Ancylostoma*. In two groups treated with 1.25 c.c. carbon tetrachloride and 1.8 c.c. carbon tetrachloride the percentage of male *Ancylostoma* expelled was greater than the percentage of female

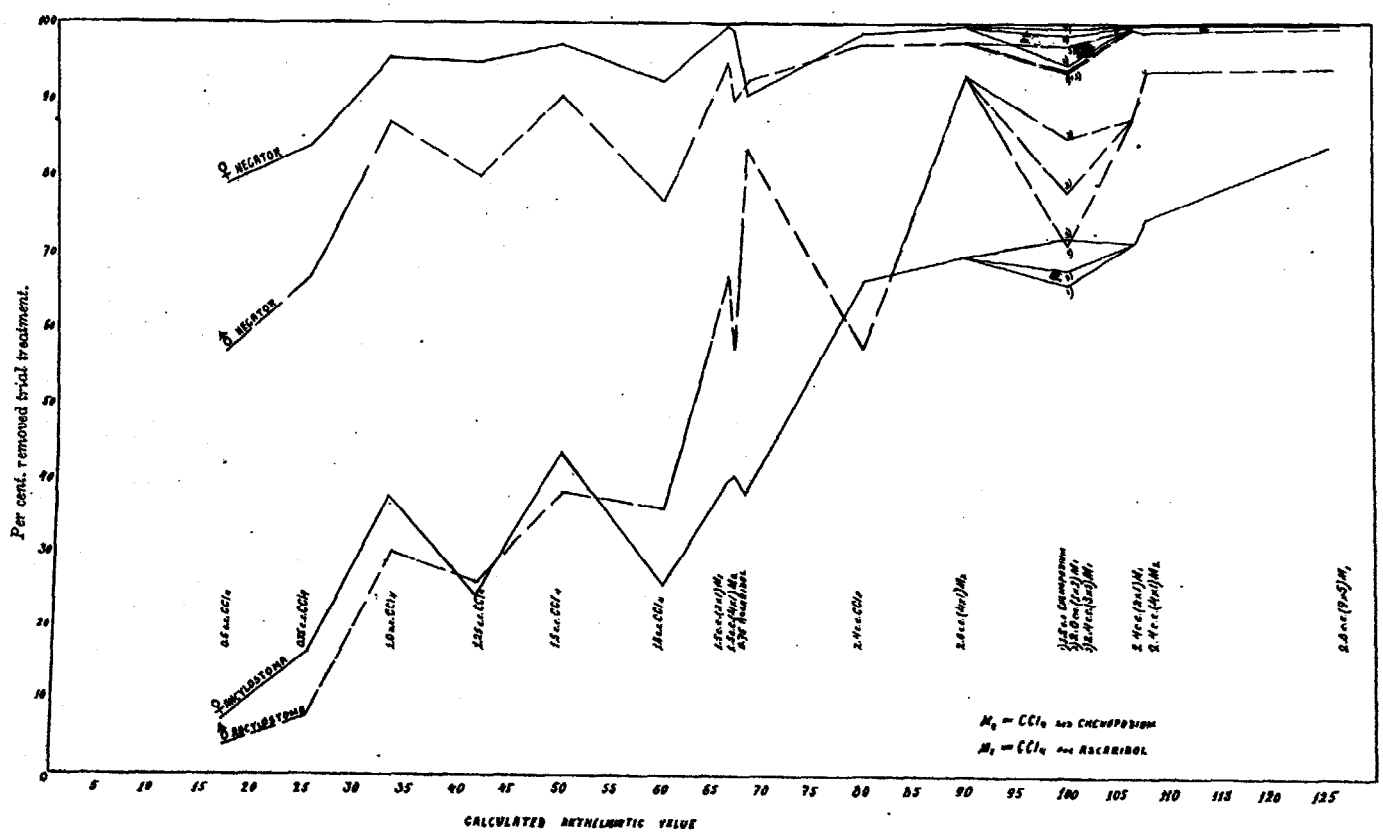

FIG. 1. Anthelmintic efficiency, by species and sex, of varying doses of carbon tetrachloride, oil of chenopodium, ascaridol, and combinations of these drugs. Based on Table VIII.

Ancylostoma. However, it is noteworthy that the five groups with higher percentage efficiency for female *Ancylostoma* than for male *Ancylostoma* were all treated with carbon tetrachloride alone, and that the three lowest doses of carbon tetrachloride used gave this selective action. In considering Fig. 1, one can do no better than quote from Darling, Barber, and Hacker (1), who based their findings on the use of oil of chenopodium and thymol:

> Lower doses of vermicide, as compared with the higher doses, are more effective against the less resistant forms of worms. These lower doses, however, are relatively ineffective, as compared with the higher doses, against the more resistant forms. The difference between the effects of vermicide on the less resistant and the more resistant forms, respectively, becomes less as the dose is increased. Finally the larger doses of vermicide are generally of particular use in getting rid of the more resistant forms.

It will be noted that the sex selectivity of carbon tetrachloride for females is much more marked in *Necator* than in *Ancylostoma*, but that the sex selectivity of ascaridol and oil of chenopodium for males is more marked in *Ancylostoma* than in *Necator*. From a study of the data in hand it is estimated that from thirty to thirty-five per cent. of a mixture of carbon tetrachloride and chenopodium must be oil of chenopodium in order to insure an equal elimination of male and female *Necator*. Probably a much lower percentage of oil of chenopodium will equalize the male and female *Ancylostoma* efficiencies, although in the face of Sawyer's reports of inefficiency of carbon tetrachloride and the relatively low rates encountered in the present work, an increase, rather than a decrease in the percentage of oil of chenopodium used, may be necessary. Sawyer (14) has returned to the use of oil of chenopodium alone in areas of *Ancylostoma* infestation.

Since, with the dosages and combinations used, male *Necator* and female *Ancylostoma* have proved to be the most resistant forms in the respective species the efficiency curves of these two forms have been transferred to Fig. 2, together with the calculated efficiency and toxicity curves from Table VIII. It should be noted that Smillie's suggested dose of 1.5 c.c. (2 x 1)M_1, with a very low toxicity value gives a high *Necator* efficiency, but is relatively ineffective for *Ancylostoma.* Of the three combinations rating one hundred theoretical efficiency, the oil of chenopodium treatment ranks the highest theoretical toxicity and the lowest efficiency for both *Necator* and *Ancylostoma,* whereas the 2.4 c.c. (2 x 1) M_1 ranks lower in theoretical toxicity and higher in efficiency for both *Necator* and *Ancylostoma* than does the dose of 2.0 c.c. (1 x 1) M_1.

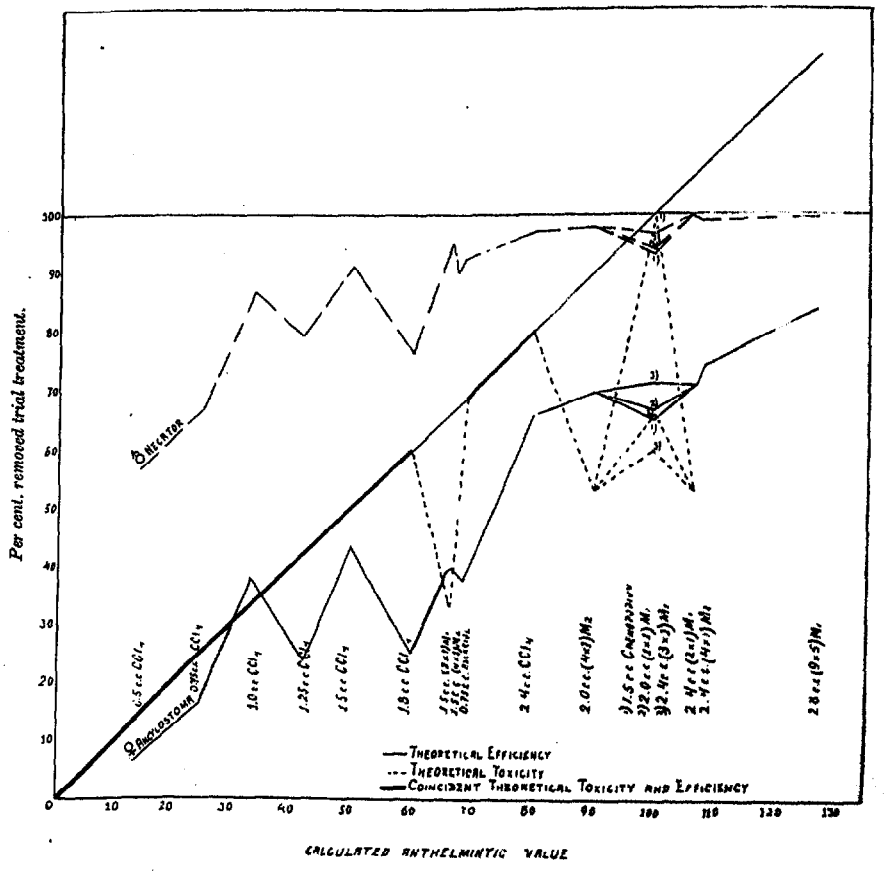

FIG. 2. Comparison of experimental efficiency for male *Necator* and female *Ancylostoma* with theoretical efficiency and theoretical toxicity. Based on Table VIII and Fig. 1. (M_1 is mixture of carbon tetrachloride and chenopodium; M_2, carbon tetrachloride and ascaridol.)

Figure 3 is still another presentation of the data of Table VIII, the upper percentage in each square being the efficiency rate for *Ancylostoma* and the lower for *Necator*. From this it is again apparent that 1.5 c.c. (2 x 1) M_1 is the minimum efficient combination for *Necator*, and that the minimum dose giving at least 80 per cent. efficiency for *Ancylostoma* is 2.4 c.c. (2 x 1) M_1. This is the dosage selected for use in Paraguay, where *Ancylostoma* form approximately 7 per cent.

of the hookworm infestation. (The values recorded under 1.6 c.c. carbon tetrachloride and .5 c.c. oil of chenopodium were disregarded, as this value is based on ascaridol treatment, and the price of ascaridol is prohibitive for field work).

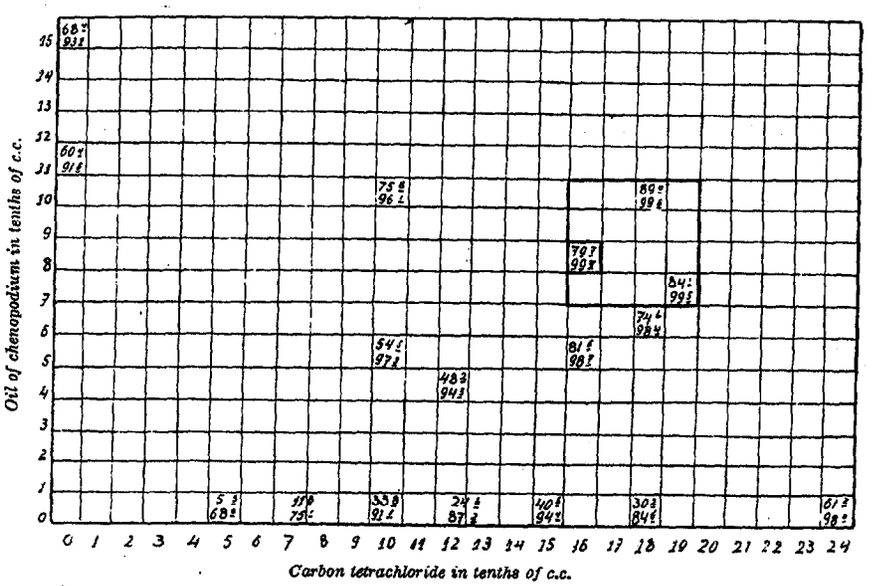

FIG. 3. Anthelmintic efficiency for total *Ancylostoma* and total *Necator*, as influenced by variation in combination of carbon tetrachloride and oil of chenopodium and in total dosage. Based on data of Table VIII. (The upper figures in each square are per cent. efficiencies for *Ancylostoma;* the lower figures for *Necator*.)

In order to simplify the study of sex and species resistance to different types of anthelmintic action, Table IX—*A* was prepared, classi ying all groups into three classes according to drug or combination of drugs used in treatment, and the first class (those groups treated with combinations of carbon tetrachloride and oil of chenopodium) was further divided into two classes according to the efficacy of the treatment. The percentage of total worms removed by the test treatment of 3 c.c. of oil of chenopodium has been considered as the measure of resistance of the particular form of the drug under consideration. In this table no correction or elimination has been made for modifications in treatment other than the drug administered. Figs. 4, 5, 6 and 7 are based on Table IX—*A*. From Fig. 4, it is seen that the decreasing

TABLE IX—*A*.

Sex and species resistance to different types of anthelmintic action.—A.

Group Nos.	Anthelmintic.	Worms recovered.								Per cent. resistant to trial treatment.				
		Necator.				*Ancylostoma.*				Total.	*Necator.*		*Ancylostoma.*	
		Female.		Male.		Female.		Male.						
		Total.	Test treatment.	Total.	Test treatment.	Total.	Test treatment.	Total.	Test treatment.		F.	M.	F.	M.
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*
1–2–3–4–12 13–14–15–16 17–27–28–	Efficient combination CCl_4 and Chen. (over 95%)	24,184	146	24,020	589	2,202	584	1,569	233	3.0	0.6	2.5	26.5	14.9
11–26	Inefficient combination CCl_4 and Chen. (less than 95%)	2,989	23	2,846	212	168	109	141	51	6.4	0.8	7.4	64.9	36.2
18–19–20–21 5–6–7–8–9–10	CCl_4 alone	10,412	908	9,841	2,160	725	501	674	507	18.8	8.7	21.9	69.1	75.2
22–23–24–25	Chenopodium and ascaridol alone	1,415	219	1,353	184	62	35	55	25	16.0	15.5	13.6	56.5	45.5

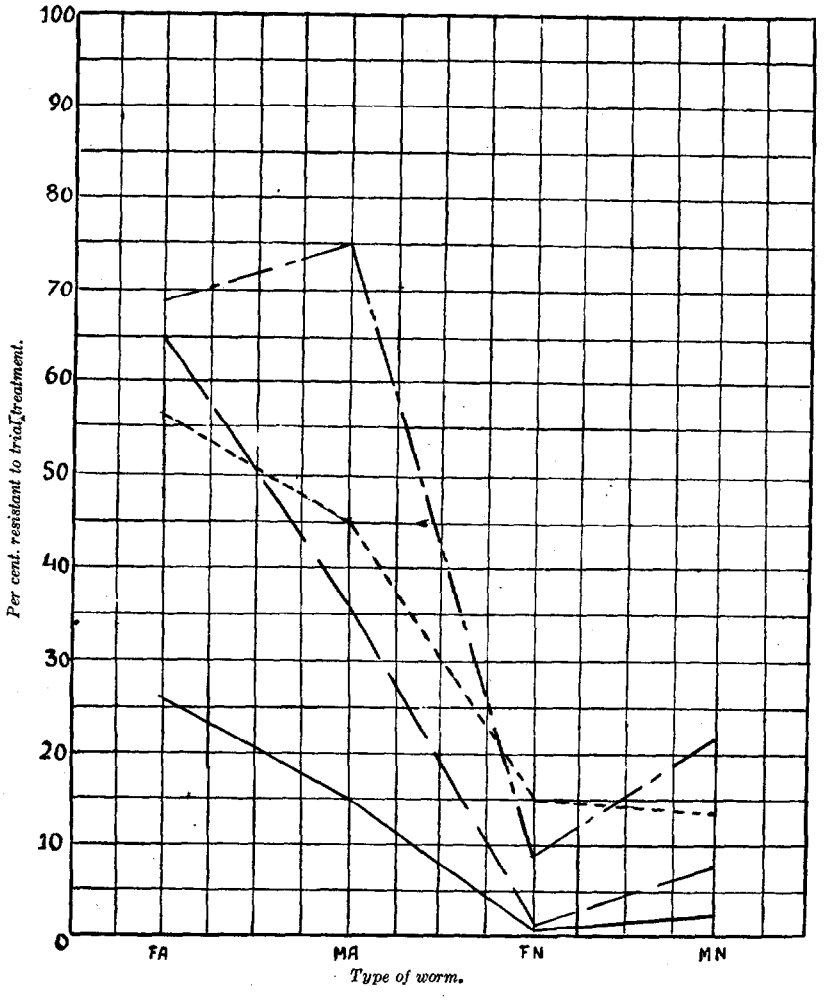

FIG. 4. Sex and species resistance to different types of anthelmintic action. Data from Table IX—*A*. *FA*, female *Ancylostoma; MA*, male *Ancylostoma; FN*, female *Necator; MN*, male *Necator*.

——— Efficient combination, CCl_4 and Chenopodium (95 per cent. of all worms expelled).

— — — Inefficient combination, CCl_4 and Chenopodium (Less than 95 per cent. of all worms expelled).

— - — - CCl_4 alone. (Combined results of all dosages used, 0.5 to 2.4 c.c.)

- - - - - - - - Ascaridol and Chenopodium. (Combined results.)

order of resistance to oil of chenopodium and ascaridol is that originally reported by Darling, viz: female *Ancylostoma*, male *Ancylostoma*, female *Necator*, male *Necator*, although the selectivity between species is greater than that between sexes, and the selectivity for male *Ancylostoma* is greater than that for male *Necator*. With tetrachloride alone the order is changed and becomes, male *Ancylostoma*, female *Ancylostoma*, male *Necator*, female *Necator*, and here again the species selectivity is greater than the sex selectivity, but the selectivity for female *Necator* is greater than for female *Ancylostoma*. With combinations of carbon tetrachloride and oil of chenopodium (both groups) we find a peculiar mixing of the two previous orders, viz: female *Ancylostoma*, male *Ancylostoma*, male *Necator*, female *Necator*. This order would indicate that in the combinations used, the sex selectivity of oil of chenopodium predominated in the case of *Ancylostoma duodenale* and that of carbon tetrachloride in the case of *Necator americanus*.

Figure 5 presents the same data as Fig. 4, but is plotted on arithlog grid. Here the slopes of the lines joining any two points indicates the rate of change. This brings out the fact that the difference in sex selectivity between the two species is greater with carbon tetrachloride and is less with oil of chenopodium than appeared to be the case in Fig. 4. Other interesting facts can be deduced by the same method. Fig. 6 is a rearrangement of Fig. 5 in which the species selectivity by sex is indicated by the slopes of the lines. From this it is apparent that there is the same species selectivity for males as females when oil of chenopodium is the drug used. With carbon tetrachloride the species selectivity is greater for females than for males. In both combinations of the two drugs the species selectivity was markedly greater for females than for males. This was more noticeable for the inefficient combinations. From Fig. 7, it is clear that the decreasing order of slope of the curves between carbon tetrachloride and efficient combination, and between efficient combination and oil of chenopodium is female *Necator*, male *Necator*, male *Ancylostoma*, female *Ancylostoma*. This is interesting, as it indicates that, although the statement previously quoted, that lower doses of vermicide as compared with higher doses are more effective against the less resistant forms, holds for actual values, that the rate of decrease of resistance to larger doses is greater for the less resistant forms. Fig. 7 also emphasizes the point that the sex selectivity of carbon tetrachloride is greater for *Necator* than for *Ancylostoma*, but that of oil of chenopodium is greater for *Ancylostoma*.

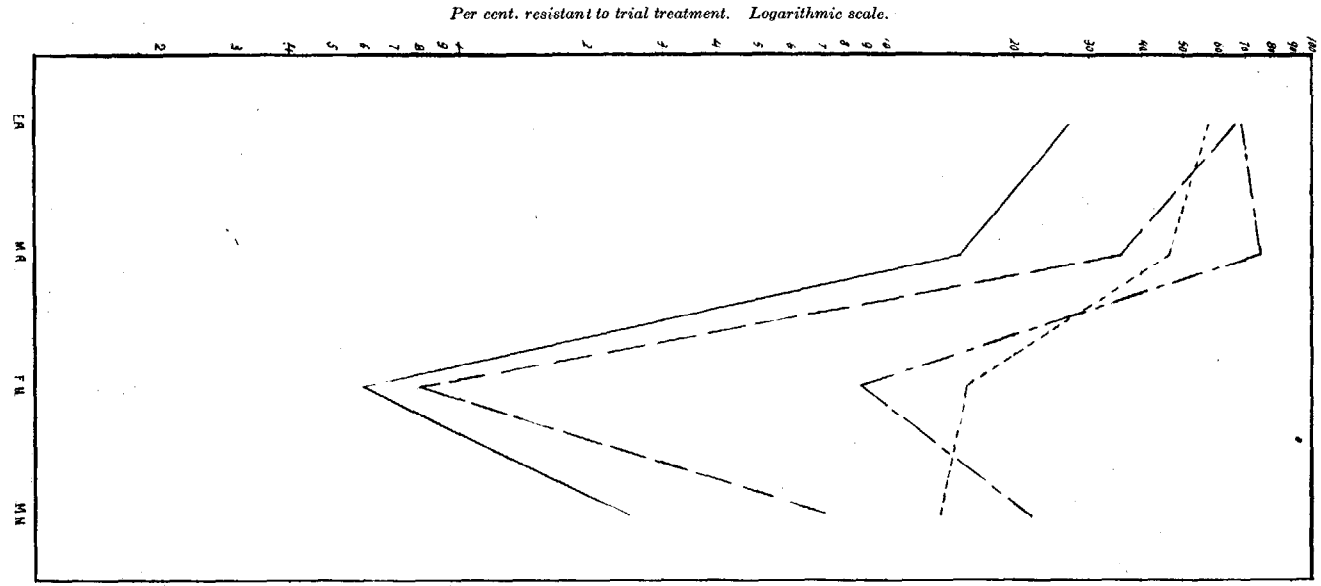

FIG. 5. Sex and species resistance to different types of anthelmintic action plotted on arithlog grid. Data from Table IX—*A*. *FA*, female *Ancylostoma; MA*, male *Ancylostoma; FN*, female *Necator; MN*, male *Necator*.

——— Efficient combination, carbon tetrachloride and chenopodium, (95 per cent. of all worms expelled).
— — — Inefficient combination, carbon tetrachloride and chenopodium, (less than 95 per cent. of all worms expelled).
— - — - Carbon tetrachloride alone (combined results of all dosage used 0.5 to 2.4 c.c.
- - - - - - - - - Ascaridol and chenopodium (combined results).

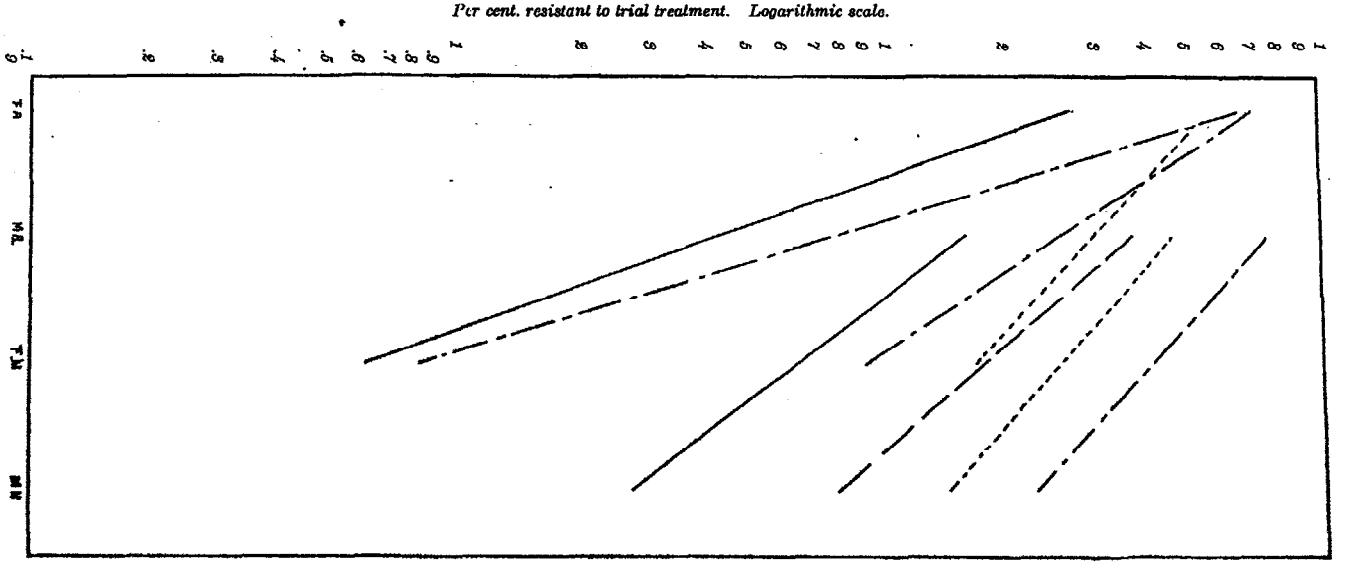

FIG. 6 Species resistance to different types of anthelmintic action for male and female hookworms. Data from IX—*A* and Fig. 5. *FA*, female *Ancylostoma*; *MA*, male *Ancylostoma*. *FN*, female *Necator*, *MN*, male *Necator*.

- · · · · Efficient combination, carbon tetrachloride and oil of chenopodium. (95 per cent. of all worms expelled.)
— — Inefficient combination, carbon tetrachloride and oil of chenopodium. (Less than 95 per cent. of all worms expelled.)
— — — Carbon tetrachloride alone. (Combined results of all dosage used, 0.5 to 2.4 c.c.)
---------- Ascaridol and chenopodium. (Combined results.)

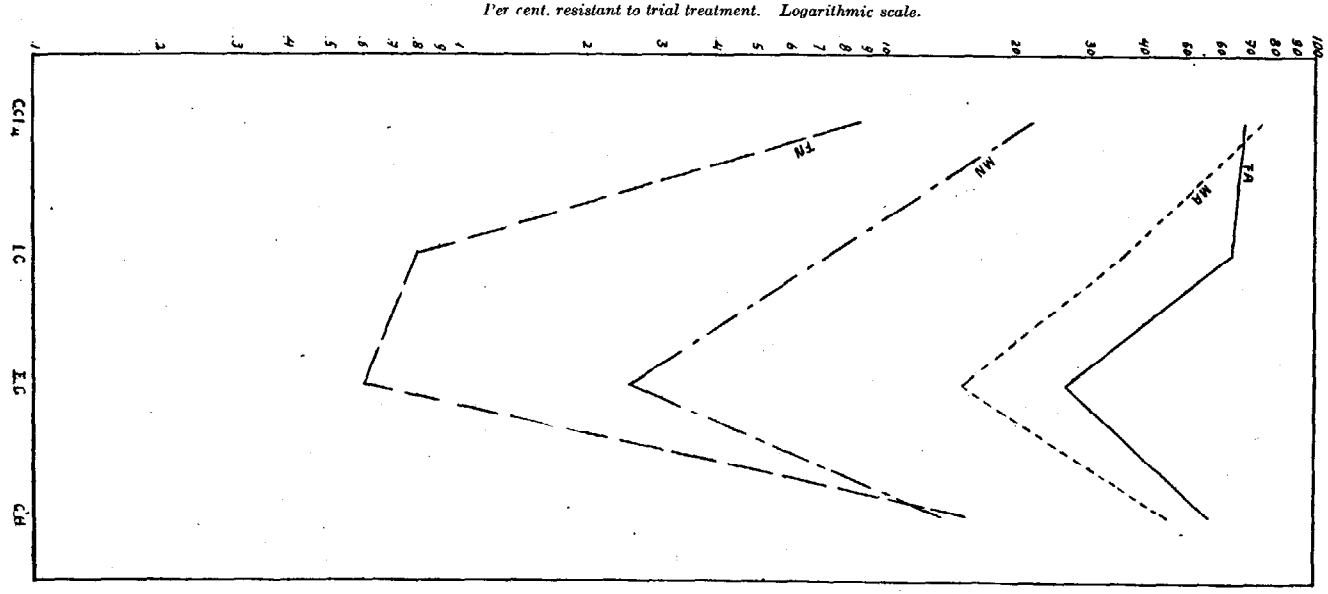

FIG. 7. Sex and species resistance to different types of anthelmintic action; rearrangement of Fig. 5 from Table IX—*A*. *FA*, female *Ancylostoma; MA*, male *Ancylostoma; FN*, female *Necator; MN*, male *Necator*.

CCl_4, all doses of carbon tetrachloride used alone.
IC, inefficient combination of carbon tetrachloride and oil of chenopodium. (Less than 95 per cent. of all worms expelled.)
EC, efficient combination of carbon tetrachloride and oil of chenopodium. (95 per cent. of all worms removed.)
CH, Ascaridol and chenopodium combined results.

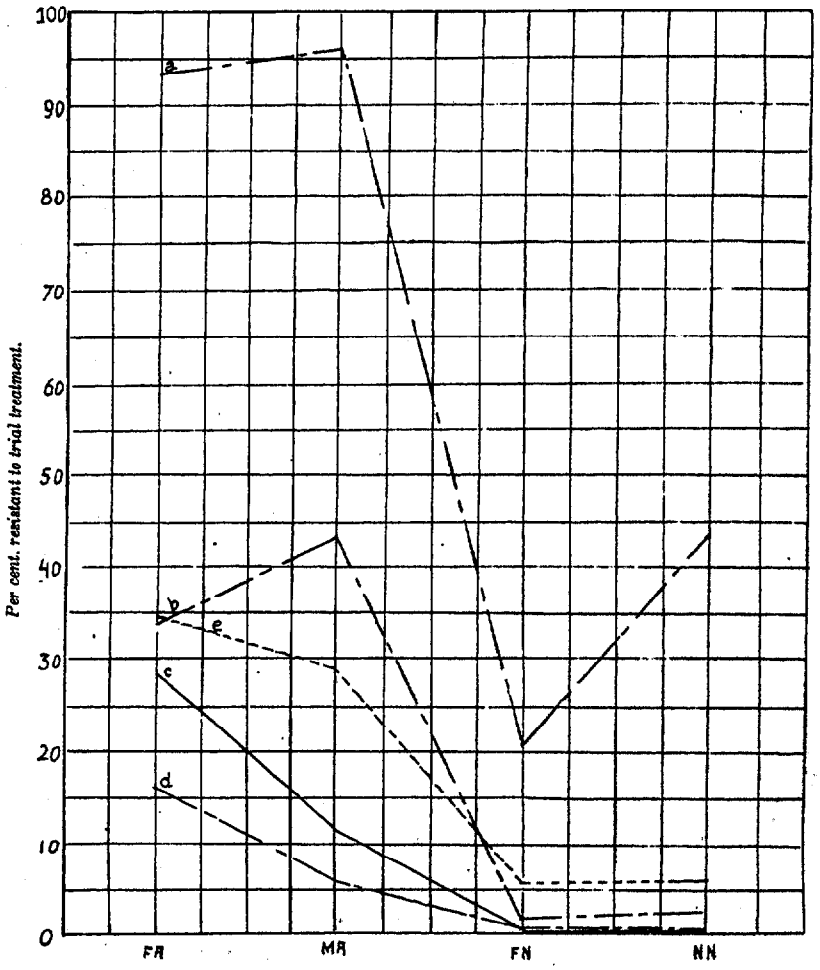

FIG. 8. Sex and species resistance, as influenced by type and dose of anthelmintic. Based on Table IX—*B*. *FA*, female *Ancylostoma*, *MA*, male *Ancylostoma*: *FN*, female *Necator*; *MN*, male *Necator*.

a, carbon tetrachloride in adult dose of 0.5 c.c.
b, carbon tetrachloride in adult dose of 2.4 c.c.
c, 2 x 1 combination in adult dose of 2.4 c.c.
d, 9 x 5 combination in adult dose of 2.8 c.c.
e, oil of chenopodium in adult dose of 1.5 c.c.

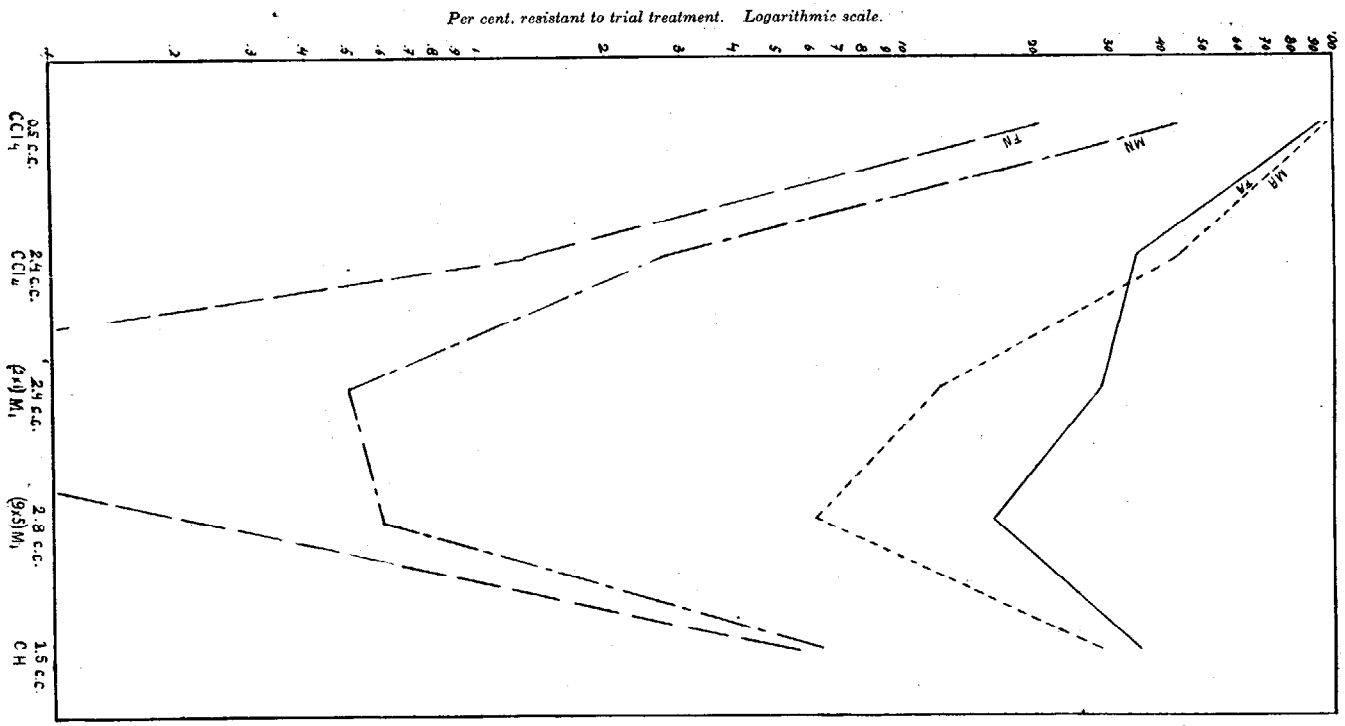

FIG. 9. Sex and species resistance, as influenced by type and dose of anthelmintic; rearrangement on arithlog grid of data from Table IX—*B* used in Fig. 8. *FA*, female *Ancylostoma; MA*, male *Ancylostoma; FN*, female *Necator; MN*, male *Necator*.

CCl_4, carbon tetrachloride; M_1, mixture of carbon tetrachloride and oil of chenopodium; CH, oil of chenopodium.

Table IX—*B* has been prepared for the more detailed study of anthelmintic action in groups where a given dose was administered. In considering Table IX—*B* and Figs. 8 and 9 based thereon, reference should be made to Table VIII which gives the number of *Ancylostoma* in each group on which resistances were calculated.

TABLE IX—*B*.

Sex and species resistance to different types of anthelmintic action.—B.

Group No.	Drug.	Adult dose.	Per cent. resistant to trial treatment.			
			Necator.		*Ancylostoma*.	
			Female.	Male.	Female.	Male.
A	*B*	*C*	*D*	*E*	*F*	*G*
9	CCl_4	0.5	20.5	43.4	93.2	96.2
21	CCl_4	2.4	1.3	2.7	34.3	43.2
12	$(2 \times 1)M_1$	2.4	0.0	0.5	28.6	12.0
3	$(9 \times 5)M_1$	2.8	0.2	0.6	15.8	6.1
22	Chenopodium	1.5	5.6	6.5	34.5	28.6

Figure 8 is similar to Fig. 4, except that male *Necator* shows a slightly greater resistance than does female *Necator* to oil of chenopodium. This finding is contrary to those of other workers and of other groups in this series. Fig. 9, plotted on arithlog grid confirms the other findings of Fig. 7.

Table X presents differences in experimental efficiency encountered in groups treated with equal doses of anthelmintic, but with modifications, such as delayed purge, divided dose, repeated purge, normal salt solution and type of individuals in the group. In considering *Ancylostoma* rates, the data of column *L* should be carefully considered. From an examination of this table it will be seen that when carbon tetrachloride or a combination of carbon tetrachloride and oil of chenopodium was administered in the same manner to adults and to children, that the efficiency rates were always slightly better for children, even though the degree of infestation was less in the child groups. The repeated purge, used in but one group, was without apparent marked effect on the efficiency rates. The divided dose and delayed purge gives superior results with oil of chenopodium, which are not apparent for such combinations of carbon tetrachloride and oil of chenopodium, as were used in these tests. Ascaridol gave good

results with simultaneous purge which did not follow when normal saline solution was given three hours after the simultaneous purge.

TABLE X.

Effect of anthelmintic efficiency of factors other than the character and dose of anthelmintic employed.

Group No.	Drug.	Adult dose.	Purge.	Experimental efficiency.						Remarks.	No. *Ancylostoma* in group.
				Necator.			*Ancylostoma.*				
				F.	M.	T.	F.	M.	T		
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*
6	CCl_4	1.0	S	95.2	87.9	91.5	32.9	27.8	30.3	Adults	182
20	CCl_4	1.0	S	95.4	82.6	89.0	54.2	38.5	46.3	Children	50
5	CCl_4	1.5	S	96.5	90.3	93.4	30.9	25.0	27.9	Adults	124
18	CCl_4	1.5	S	99.0	93.4	96.2	58.2	54.3	56.2	Children	101
19	CCl_4	1.5	SR	98.6	86.2	92.4	50.0	51.5	50.7	Children	65
11	$(2 \times 1)M_1$	1.5	S	99.5	94.1	96.8	33.1	66.7	49.9	Adults	220
14	$(2 \times 1)M_1$	1.5	S	100.0	100.0	100.0	77.8	100.0	88.9	Children	29
13	$(2 \times 1)M_1$	1.5	DD	96.4	95.2	95.8	59.3	82.4	70.8	Children	88
15	$(2 \times 1)M_1$	1.5	SS	99.4	95.8	97.6	66.7	70.0	68.3	Children	28
24	Ascar.	.75	S	90.3	92.9	91.6	37.5	83.3	60.4	Children	14
25	Ascar.	.75	SS	78.1	76.5	77.3	10.0	31.6	20.8	Children	29
23	Chen.	1.5	S	86.1	93.0	89.5	26.7	56.2	41.4	Children	31
22	Chen.	1.5	DD	94.4	93.5	93.9	65.5	71.4	68.4	Children	43
1	$(3 \times 1)M_1$	2.4	D	99.2	98.3	98.7	72.9	82.0	77.4	Adults	965
2	$(3 \times 1)M_1$	2.4	S	99.4	97.4	98.4	71.8	77.4	74.6	Adults	897
16	$(2 \times 1)M_1$	2.4	SS	100.0	98.7	99.3	77.8	95.3	86.5	Children	124
17	$(2 \times 1)M_1$	2.4	DD	99.2	92.3	95.7	77.8	92.3	85.0	Children	40
12	$(2 \times 1)M_1$	2.4	S	100.0	99.5	99.7	71.4	88.0	79.7	Adults	85

D = Delayed purge.
DD = Delayed purge and divided dose.
S = Simultaneous purge.
SS = Simultaneous purge followed after 3 hours by 1 quart of normal salt solution.
SR = Simultaneous purge followed after 3 hours by magnesium sulphate in 25% solution.
M_1 = Carbon tetrachloride and oil of chenopodium.
M_2 = Carbon tetrachloride and ascaridol.

TABLE XI.

Relation of time of administration of purge to time of expulsion of hookworms.

Group No.	Trial treatment.						Per cent. efficiency trial treatment.
	Drug.	Adult dose.	Purge.	Hookworms expelled.			
				Total.	1st 24 hrs.	Per cent. 1st 24 hrs.	
A	*B*	*C*	*D*	*E*	*F*	*G*	*H*
1	(3 x 1)M_1	2.4	D	10,267	8,860	86.3	96.7
17	(2 x 1)M_1	2.4	DD	988	812	82.2	95.5
13	(2 x 1)M_1	1.5	DD	598	442	73.9	92.0
12	(2 x 1)M_1	2.4	S	1,853	1,237	66.8	98.9
3	(9 x 5)M_1	2.8	S	10,805	6,642	61.5	98.9
2	(3 x 1)M_1	2.4	S	10,211	5,831	57.1	96.3
4	(1 x 1)M_1	2.0	S	7,681	4,306	56.1	94.9
11	(2 x 1)M_1	1.5	S	3,676	1,912	52.0	94.2
28	(4 x 1)M_2	2.4	S	3,501	1,803	51.5	98.8
22	Chen.	1.5	DD	370	185	50.0	91.1
15	(2 x 1)M_1	1.5	SS	473	226	47.8	95.6
21	CCl_4	2.4	S	1,158	462	39.9	94.7
27	(4 x 1)M_2	2.0	S	2,387	935	39.2	97.4
6	CCl_4	1.0	S	1,852	668	36.1	86.3
18	CCl_4	1.5	S	1,541	543	35.2	93.6
14	(2 x 1)M_1	1.5	S	677	224	33.1	99.4
5	CCl_4	1.5	S	2,553	830	32.5	90.7
10	CCl_4	1.8	S	2,707	848	31.3	83.2
19	CCl_4	1.5	SR	891	269	30.2	90.1
8	CCl_4	1.25	S	1,863	522	28.0	83.7
16	(2 x 1)M_1	2.4	SS	1,182	293	24.8	97.8
20	CCl_4	1.0	S	391	91	23.3	84.1
26	(4 x 1)M_2	1.6	S	2,073	231	11.1	92.5
7	CCl_4	0.75	S	2,324	250	10.8	69.0
24	Asc.	0.75	S	269	28	10.4	90.0
9	CCl_4	0.50	S	2,296	117	5.1	65.2
25	Asc.	0.75	SS	855	41	4.8	75.9
23	Chen.	1.5	S	928	30	3.2	88.0

D = Delayed purge.
DD = Divided dose and delayed purge.
S = Simultaneous purge.
SS = Simultaneous purge followed after 3 hours by 1 quart of normal salt solution.
SR = Simultaneous purge followed after 3 hours by magnesium sulphate in 25% solution.
M_1 = Carbon tetrachloride and oil of chenopodium.
M_2 = Carbon tetrachloride and ascaridol.

From a consideration of the entire table it is doubtful if any modification attempted in this series will give better results with combinations of carbon tetrachloride and oil of chenopodium than the simple administration of the undivided dose, together with a simultaneous purge of magnesium sulphate in concentrated solution.

The writer has previously stated (Soper, 18)* that the simultaneous administration of magnesium sulphate, when the anthelmintic used was 2.6 c.c. of a 3 x 1 mixture of carbon tetrach'oride and oil of chenopodium, caused a delayed expulsion of hookworms from the intestine, but no reduction of efficiency. Table XI presents the twenty-eight groups in this series in descending order of percentage of total hookworms expelled in the first twenty-four hours after treatment. It will be noted that the three groups treated with combinations of carbon tetrachloride and oil of chenopodium and delayed purge gave the highest percentages expelled in the first twenty-four hours.

The lowest percentages of worms expelled in the first twenty-four hours are found in these groups treated with oil of chenopodium, ascaridol and minimal doses of carbon tetrachloride, administered with simultaneous purge. The administration of salt solution and repetition of the purge in dilute solution failed to increase the percentage expelled in the first twenty-four hours.

Table XII and Figure 10 show that there is a definite delay in the

TABLE XII.

Total efficiency and time of removal as influenced by time of administration of purge.

Group No.	Drug.	Adult dose.	Per cent. first 24 hours.		Per cent. efficiency trial treatment.	
			Delayed purge.	Simultaneous purge.	Delayed purge.	Simultaneous purge.
A	*B*	*C*	*D*	*E*	*F*	*G*
22 and 23	Chenopodium	1.5	50.0	3.2	91.1	88.0
1 and 2	(3 x 1)M_1	2.4	86.3	57.1	96.7	96.3
17 and 12	(2 x 1)M_1	2.4	82.2	66.8	95.5	98.9
13 and 11	(2 x 1)M_1	1.5	73.9	52.0	92.0	94.2

time of expulsion of worms caused by the simultaneous administration of magnesium sulphate. This effect is much more marked with oil of chenopodium than with combinations of carbon tetrachloride and

* Based on Groups 1 and 2 of present series.

oil of chenopodium. The variations in total efficiency with delayed and simultaneous purge are given in Table XII. Although these differences are small, there seems to be an increased efficiency for oil of chenopodium with delayed purge and for combinations of carbon tetrachloride and oil of chenopodium with the simultaneous purge. Using the same combination of carbon tetrachloride and oil of chenopodium (2 x 1) M_1, it was observed that with increase of dosage there is an increase in the per cent. expelled in the first twenty-four hours.

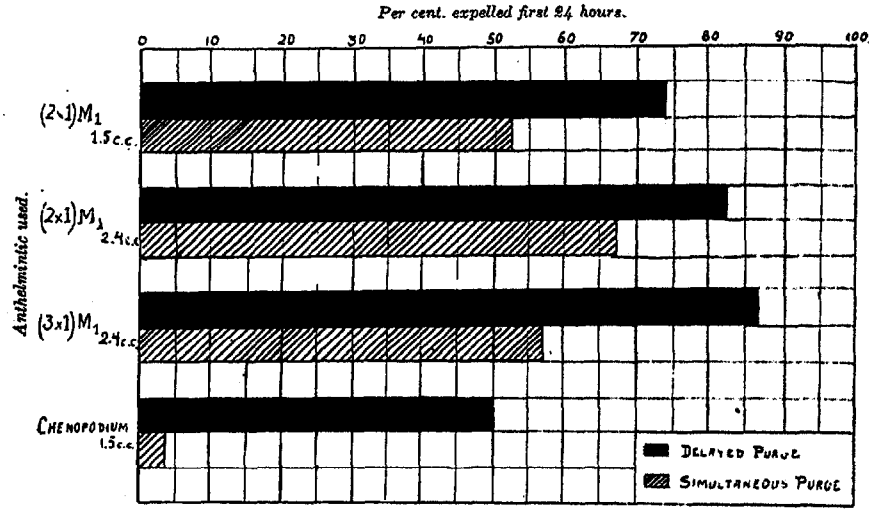

FIG. 10. Time of expulsion of hookworms, as influenced by the time of administration of the purge. Based on Table XII.

The delayed expulsion of worms which occurs with simultaneous purgation would indicate that the anthelmintic action is not immediate. Probably some hours are necessary for the anthelmintic to so affect the hookworm even after the absorption of a lethal dose, as to free its hold on the intestinal mucosa and render it unable to resist peristalsis. If the effect of the purgative has passed before the worms are sufficiently affected to be eliminated, the larger percentage of them will be left for second day findings. That the rapidity of anthelmintic action may depend upon the amount of anthelmintic administered, when the drug employed is carbon tetrachloride, is ndicated by the data of Table XIII and the statement (Leach, Haughwourt and Ash, 10) that large doses of carbon tetrachloride (presumably administered

without purgative) cause the elimination of 97 per cent. of all worms in the first twenty-four hours. It should be remembered that carbon tetrachloride has a slow purgative action, and when given in large doses should have the same effect as the administration of a delayed purge of magnesium sulphate. In contrast, oil of chenopodium has an inhibitory action on the smooth muscle of the intestine, and it is possible that larger doses of this drug will not give a similar increased rapidity of expulsion.

TABLE XIII.

Correlation between efficiency and time of removal of hookworm by carbon tetrachloride when administered with simultaneous purge.

Group No.	Adult dose.	Corrected efficiency.	Per cent. expelled first 24 hrs.
A	*B*	*C*	*D*
21	2.4	95.6	39.9
5	1.5	89.1	32.5
10	1.8	81.0	31.3
6 and 20	1.0	87.3	29.6
8	1.25	83.1	28.0
7	0.75	71.0	10.8
9	0.5	64.0	5.1

Test treatments of 3 c.c. of oil of chenopodium, given in three divided doses, with intervals of one hour, and with delayed purge given one and one half hours after the last dose, gave but 62.7 per cent. expelled in the first twenty-four hours. That oil of chenopodium is slower in action than carbon tetrachloride is also indicated by the fact that oil of chenopodium is credited with stunning rather than killing, thus causing the removal of many live worms, whereas carbon tetrachloride kills, as is evidenced by partly digested worms encountered after treatment with this drug.

Comparison of Willis flotation, Stoll egg-count and Darling worm-count methods as measures of anthelmintic efficiency.

Many recent articles on the comparative efficiency of oil of chenopodium and carbon tetrachloride have made "per cent. microscopic cures" the measure of efficiency. In the light of recent publications (D'Estefano y Vaccarezza, 4, Sawyer, et al., 14) which depreciate the value of the worm count method, some comparative studies of the results of the Willis Flotation, Stoll egg-count and Darling worm-

count methods on the same groups are of interest. Table XIV gives comparative results of the three methods as means of diagnosis of hookworm infestation in all cases of the present series. The worm

TABLE XIV.

Number and percentage of cases found infested by Stoll, Willis and worm count methods.

	Stoll.	Willis.	Worm count.
Total cases examined	419	419	419
Positive	373	362	415
Per cent. positive	88.8	86.4	99.0
Average females in negative cases	5.1	5.3	3.1*

count method revealed 12.6 per cent. higher rate of infestation than did the Willis flotation method. However, the average infestation of negative cases by any of the three methods was not over ten worms. Table XV gives comparative results for the three methods for 150 soldiers and prisoners (Groups 1 to 12), for both trial and test treatments. Here, in heavily infested groups, the Willis method missed

TABLE XV.

Positive diagnosis by Stoll, Willis and worm count methods as measures of anthelmintic efficiency, after trial treatment, based on 150 adult soldier and prisoner cases.

	Stoll.	Willis.	Worm count.
A—Positive first examination	146	148	150
B—Per cent. positive	97.3	98.7	100
C—Positive by only one method	0	0	2
D—Average females in negative cases	3.3	3.5	0
E—Negative second examination	43	52	18
F—Negatives confirmed by worm count	14	16	18
G—Negative by all 3 methods	13	13	13
H—Positive, but negative by other 2 methods	3	1	19
I—Average females in negative cases	2	2.9	0.5†
J—Negative for females by all 3 methods	17	17	17
K—Negative for females by both Willis and Stoll with positive worm count	13	13	—
L—Average females in *K*	2	2	—
M—Negative for females, but positive by other two methods	10	17	1
N—Positive for females, but negative by other two methods	3	1	15

* Calculated from Stoll egg count results.

† Calculated from Stoll egg count results.

only two cases, and these harboured but seven female worms between them. However, after trial treatment, 52 cases or 34.7 per cent. were reported negative by the Wil is method, and but 18 or 12.0 per cent. failed to reveal worms by the count method. However, the average number of females per negative case (not per missed case) was but 2.9. The Stoll method, used for diagnosis only, closely parallels the results of the Willis method.

All methods based on microscopic examination of the stool (Willis, Stoll, Lane) must fail to give a complete picture of anthelmintic action through inability to reveal species and sex selectivity of such action. Even if such methods indicate the degree of infestation, they will fail to reveal the character of infestation and its differential reduction by med cation. Table XVI shows how important this may be. If there

TABLE XVI.

Test treatment males without females of same species.

	Necator.	*Ancylostoma.*
Positive cases (worm count)	411	330
Cases with test treatment males, but no females	99	29
Maximum number of males without females	25	4

had been no infestation with *Ancylostoma duodenale*, 99 cases, or 24.3 per cent. of 411 cases would have been "cured" who in reality still harbored male *Necator*. The maximum number of males encountered without females was 25. One case was found with 48 female and 187 male *Necators*. Such results can never be revealed by methods based on microscopic examinations. Only 29, or but 8.8 per cent. of 330 cases, harboring *Ancylostoma* were found to harbor males on test treatment, without accompanying females. As before noted, there seems to be less sex selectivity of carbon tetrachloride for *Ancylostoma* than for *Necator*.

Table XVII shows at a glance how unreliable the Willis method may be as an indication of the reduction of infestation in heavily

TABLE XVII.

Per cent. anthelmintic efficiency as indicated by Willis flotation, Stoll egg count and Darling worm count methods with 150 heavily infested adults.

	Willis microscopic.	Stoll egg count.	Worm count.
First examination	148	1,233,900	58,088
Second examination	98	111,500	5,255
Per cent. reduction of total	33.8	91^0	91^7

infested groups. The results for the Stoll method have been arrived at directly as per cent. reduction in egg-count without reference to the number of eggs per female per gram of feces. The Willis method will probably give too low a measure of efficiency in highly infested groups and too high a percentage of cures in lightly infested groups. It is doubtful if the Stoll method in its present state of development will consistently give such close results in small groups as are found in this case, as the writer has encountered wide variation in group averages of the number of eggs per gram per female encountered on worm count.

Sawyer et al. (14) say: "We were sadly disappointed, however, for only 23.1 per cent. of the patients who received carbon tetrachloride in this amount (3 c.c.) were cured, while 46.7 or twice as many of those receiving the standard course of two treatments with 1.5 c.c. of oil of chenopodium were freed from infection." (Cures based on Willis examination in *Ancylostoma* area.) Similar results were secured in the present series, if judged by per cent. cures. Carbon tetrachloride in 2.4 c.c. dosage gave but 30 per cent. cures (worm count) for *Ancylostoma*, while oil of chenopodium gave 54.6 per cent. cures. However, the percentage total of Ancylostomas removed in the group with carbon tetrachloride was 61.2 and with oil of chenopodium but 68.4.

Toxicity in controlled groups and field campaign.

No estimate can be made of the comparative toxicity of the various anthelmintics used, as careful records of minor symptoms were not kept. It is noteworthy that only one case was eliminated because of vomiting, and that neither with trial nor test treatments did any case of intoxication occur which necessitated calling the writer, or an other physician. The only group complaint that came to notice as to severity of medication was from the penitentiary group treated with 2.4 c.c. of a 2 x 1 combination of carbon tetrachloride and oil of chenopodium.

The factors which probably caused the absence of intoxication were:

The inability of any group to secure alcohol;
The low degree of Ascaris infestation;
The absence of severe clinical cases of hookworm disease among those treated;
The sufficiency and high carbohydrate content of the diets of the various groups.

The approximate diet lists of the various groups during the period of these examinations were:

For soldiers: beans, beef, hominy, oranges and tangerines, Paraguayan tea;
For prisoners: beef, rice, beans, hominy, oranges and tangerines, Paraguayan tea;
For orphans: beef, rice, potatoes, mandioca, bread, oranges and tangerines.

Although, on paper, the "prisoner" diet compares favorably with that of the other groups, such is not the case. Possibly the group complaint mentioned above has some relation to inadequacy of diet preceding treatment. It should also be remembered that all cases received purgative doses of magnesium sulphate twenty-four hours after treatment. The writer is unable to state whether this practice affected the toxicity in any way.

Every efficient anthelmintic used has produced fatal cases of intoxication when adopted for field work on a large scale. Lambert had treated over 40,000 cases with carbon tetrachloride before encountering serious cases of intoxication. Therefore the absence of serious symptoms in this small group of 419 cases can not be taken to indicate the safety of the drugs used for field work. All cases received the test treatment, based on an adult dose of 3 c.c. of oil of chenopodium, without the occurrence of serious intoxications, and yet no one would advise the use of such a dose in a general campaign. The following data regarding the use of combinations of carbon tetrachloride and oil of chenopodium in the Campaña Sanitaria coincidently with the present series of cases is given to indicate the difficulties attending their use in field work.

From March 1 to July 1, 9,400 treatments were administered in Asunción, using a 3 x 1 mixture of carbon tetrachloride and oil of chenopodium in an adult dose of 2.4 c.c., followed by delayed purge two hours after treatment. During this time, one fatal case * of intoxication occurred. Another case, a child of 4 years, with a heavy *Ascaris* infestation, presented symptoms of intestinal obstruction and died on the 5th day.

From July 1 to November 1, 26,800 treatments were given with a 2 x 1 mixture of carbon tetrachloride and oil of chenopodium in an individual adult dose of 2.4 c.c., with simultaneous purge. During this period the writer has seen three cases of intoxication, undoubtedly due to carbon tetrachloride. One had imbibed freely the evening

* Chronic alcoholic who took rum on day of treatment and 'agua chloroformada' the following day.

before treatment, one the morning of treatment and the third, the second day after treatment. All recovered.

During the period March 1 to November 1, sixty-three women, pregnant from 2 to 8 months, were treated with 2.4 c.c. carbon tetrachloride, some with delayed, others with simultaneous purge. No serious consequences which could be attributed to the treatment have been encountered. Two abortions, one at 2 months and one at 5 months, have occurred in this group, one 10 days, the other 12 days after treatment.

Summary and conclusions.

1. Four hundred and nineteen cases were treated with carbon tetrachloride, oil of chenopodium or a combination of these two drugs. Efficiency rates of such treatments were calculated for species and sex on the basis of per cent. removed by first treatment, as tested by the administration of three c.c. of oil of chenopodium.

2. The average hookworm infestation among Paraguayan soldiers and prisoners is high; among boys and girls of the asylum a much lower degree of infestation exists. Seven per cent. of 82,856 hookworms classified were *Ancylostoma duodenale*. The present ratio between *Ancylostoma* and *Necator* is probably due to three factors: early introduction of *Ancylostoma* by Spanish colonists; the absence of negro slaves; and the occupation of Paraguay by the Brazilian army with its known heavy *Necator* infestation, following the Paraguayan war.

3. Ascaris infestation in Paraguay is relatively low, (11.7 per cent.), being but one fourth that of *Trichuris* (43.4 per cent.). No judgment of the relative value of the anthelmintics used as ascaricides can be made from the present study. The efficiency of all combinations used is low for *Trichuris*.

4. Correction of total efficiency rates for distribution of worm population by species and sex of each group failed to cause over 2.5 per cent. difference in such rate of any group. Correction of species efficiency rates for equal sex distribution caused no appreciable difference in *Necator* rates, where the number of worms was relatively large; a maximum change of 3.3 per cent. occurred in certain groups in *Ancylostoma* rates where the number of worms was small.

5. Oil of chenopodium and carbon tetrachloride both possess a species and sex selective action on *Necator* and *Ancylostoma*. Both are more active against *Necator* than against *Ancylostoma*. Oil of chenopodium is more efficient for males than for females; carbon

tetrachloride is more efficient for females than for males. The decreasing order of resistance is as follows:

Oil of chenopodium	*Carbon tetrachloride*	*2 x 1 combination*
Female *Ancylostoma*	Male *Ancylostoma*	Female *Ancylostoma*
Male *Ancylostoma*	Female *Ancylostoma*	Male *Ancylostoma*
Female *Necator*	Male *Necator*	Male *Necator*
Male *Necator*	Female *Necator*	Female *Necator*

6. The species selectivity of both oil of chenopodium and carbon tetrachloride is greater than the sex selectivity. The selectivity of oil of chenopodium for males is more marked with *Ancylostoma* than with *Necator*, whereas the selectivity of carbon tetrachloride for females is more marked with *Necator* than with *Ancylostoma*. A 3 x 1 mixture of carbon tetrachloride and oil of chenopodium has slightly less oil of chenopodium than is necessary, in the dosages used, to overcome the female selectivity of carbon tetrachloride in *Necator*, but somewhat more than is required for the same purpose with *Ancylostoma*.

7. Simultaneous administration of concentrated magnesium sulphate with combinations of carbon tetrachloride and oil of chenopodium, such as used in this study, delays the expulsion of worms, but does not impair the ultimate anthelmintic result. The larger the dose of carbon tetrachloride administered with simultaneous purge, the larger is the percentage of worms expelled in the first twenty-four hours. Oil of chenopodium gives a delayed expulsion in comparison with carbon tetrachloride.

8. One and a half cubic centimeters of a two to one mixture of carbon tetrachloride in undivided dose and with simultaneous purge of magnesium sulphate in concentrated solution gave very high efficiency for *Necator*. This dosage should be sufficient for treating lightly infested areas where *Ancylostoma* does not occur. Areas with heavy infestation of *Necator* should never require a larger adult dose than 2.5 cubic centimeters of this combination.

9. The best results were obtained for *Ancylostoma* with 2.8 c.c. of a 9 x 5 mixture of carbon tetrachloride and oil of chenopodium (1.8 c.c. carbon tetrachloride and 1.0 c.c. oil of chenopodium). From a study of the efficiency curve a dosage of 3.5 c.c. of a two to one combination would be required to give the same efficiency for *Ancylostoma*, as is secured for *Necator* with 2.4 c.c. This dosage is probably above the limit of safety for field work, but should be applicable to controlled institutional groups. Further controlled groups are re-

quired to determine the proper combination and dosage of carbon tetrachloride and oil of chenopodium for maximum efficiency for *Ancylostoma* within limits safe for wide application in the field.

10. The Willis flotation method is not a safe criterion of efficiency of anthelmintic action.

11. The Stoll egg-count method gave the same per cent. total reduction in hookworm infestation in 150 cases following trial treatment, as did the more laborious worm-count method.

12. The worm-count method was shown to be superior to the Willis and Stoll methods as a means of diagnosis of the presence of hookworm. The method is *indispensable for the determination of the degree and character of infestation* and the study of *sex and species selectivity of anthelmintics.*

13. No serious toxic symptoms were noted in 419 cases of this series. The maximum doses administered were: 3 c.c. oil of chenopodium; 2.4 c.c. carbon tetrachloride; and 2.8 c.c. of a 9 x 5 mixture of carbon tetrachloride and oil of chenopodium.

14. Five serious (two fatal) cases (four alcoholics and one child with heavy *Ascaris* infestation) have been encountered in 36,000 treatments with an adult dose of 2.4 c.c. of 3 x 1 and 2 x 1 combinations of carbon tetrachloride and oil of chenopodium.

15. Pregnant women may be treated with moderate doses of carbon tetrachloride without danger.

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